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(54) Title: A METHOD FOR TREATING HERPES VIRUSES

(57) Abstract: The present invention relates to a method for selecting an anti-herpes viral compound and a method for selectively inhibiting herpesvrus in a human host in need of such treatment. The present invention relates to a method for selecting an anti-herpes viral compound and a method for selectively inhibiting herpsvrus in a human host in need of such treatment.

A METHOD FOR TREATING HERPES VIRUSES

FIELD OF THE INVENTION

The present invention relates to a method for selecting an anti-herpes viral compound and a method for selectively inhibiting herpes viruses in a human host in need of such treatment.

BACKGROUND OF THE INVENTION

The herpesviruses comprise a large family of double stranded DNA viruses. Eight of the herpes viruses, herpes simplex virus types 1 and 2 (HSV-1 and HSV-2), varicella zoster virus (VZV), human cytomegalovirus (HCMV), Epstein-Barr virus (EBV), and human herpes viruses 6, 7, and 8 (HHV-6, HHV-7, and HHV-8), have been shown to infect humans. Several of these viruses are important human pathogens.

HSV-1 is estimated to affect 100 million people in the U.S. Primary infection of HSV-1 usually occurs between the ages of one and four. Cold sores, the visible symptom, typically appear at a later age, with 20-45% of the population over the age of fifteen affected (Whitley, Clin. Intect. Dis., 26:541-555, 1998).

Genital herpes (HSV-2) is the second most common sexually transmitted disease, with approximately 22% of the U.S population infected with this virus (Fleming 1997).

VZV is the causative agent of chicken pox upon primary infection and can recur in adults as zoster.

EBV results in approximately two million cases of infectious mononucleosis in the U.S. each year. It can also cause lymphomas in immunocompromised patients and has been associated with Burkitt's lymphoma, nasopharyngeal carcinoma, and Hodgkins disease.

Infection with HCMV often occurs during childhood and is typically asymptomatic except in immunocompriomised patients where it causes significant morbidity and mortality.

HHV-6 is the causitive agent of roseola and may be associated with multiple sclerosis and chronic fatigue syndrome. HHV-7 disease association is unclear, but it may be involved in some cases of roseola. HHV-8 has been associated with Karposi's sarcoma, body cavity based lymphomas, and multiple myeloma.

These viruses are capable of residing in a latent state within the host. Reactivation of latent virus results from response to environmental stimuli (ex. UV exposure, stress,

etc.). Infections or recurrence can be life threatening in immunocompromised patients such as AIDS or transplant patients where HCMV can result in retinitis, pneumonia, and gastrointestinal disease.

The increased immunocompromised population has created an unmet medical need for antivirals against herpesviruses because current therapies do not have a sufficiently broad spectrum against this family of viruses and/or they have limited utility due to toxicity. The present invention provides a method for selectively inhibiting herpesviruses DNA polymerase with compounds that have broad spectrum activity. The method offers a distinct advantage in the treatment of patients in need, particularly immunocompromised patients at risk of infection or reactivation by many members of the herpesvirus family.

SUMMARY OF THE INVENTION

The present invention provides a method of selecting compounds that inhibit herpes viruses comprising:

a) measuring IC_{50} of a compound of interest that inhibits a wild type herpes virus,

b) measuring IC_{50} of the same compound that inhibits a binding domain mutant herpes virus which is the same strain of the wild type herpes virus,

c) comparing IC_{50} of step a with IC_{50} of step b; and

d) selecting the compound of interest wherein the IC_{50} of step b is at least 3 times greater than the IC_{50} of step a.

In above method, the order of step a and step b are interchangeable.

The present invention further provides a method of selecting compounds that inhibit herpes viruses comprising:

a) measuring IC_{50} of a compound of interest that inhibits a wild type HSV-1,

b) measuring IC_{50} of the same compound that inhibits a binding domain mutant HSV-1 which is the same strain of the wild type herpes virus,

c) comparing IC_{50} of step a with IC_{50} of step b; and

d) selecting the compound of interest wherein the IC_{50} of step b is at least 3 times greater than the IC_{50} of step a.

In above method, the order of step a and step b are interchangeable.

The present invention further provides a method of selecting compounds that inhibit herpes viruses comprising:

a) measuring IC_{50} of a compound of interest that inhibits a wild type HSV-2,

b) measuring IC_{50} of the same compound that inhibits a binding domain mutant HSV-2 which is the same strain of the wild type herpes virus,

c) comparing IC_{50} of step a with IC_{50} of step b; and

d) selecting the compound of interest wherein the IC_{50} of step b is at least 3 times greater than the IC_{50} of step a.

In above method, the order of step a and step b are interchangeable.

The present invention further provides a method of selecting compounds that inhibit herpes viruses comprising:

a) measuring IC_{50} of a compound of interest that inhibits a wild type HCMV,

b) measuring IC_{50} of the same compound that inhibits a binding domain mutant HCMV which is the same strain of the wild type herpes virus,

c) comparing IC_{50} of step a with IC_{50} of step b; and

d) selecting the compound of interest wherein the IC_{50} of step b is at least 3 times greater than the IC_{50} of step a.

In above method, the order of step a and step b are interchangeable.

The present invention further provides a method for selectively treating diseases caused by herpes viruses in a human host comprising administering a compound to a human in need of such treatment wherein said compound inhibits herpes viruses by interaction with the binding domain in the viral DNA polymerase.

The present invention further provides method for selectively inhibiting herpes viruses in a human host comprising administering a compound to a human in need of such treatment wherein IC_{50} of the compound that inhibits a binding domain mutant herpes virus is at lease 3 times greater than IC_{50} of the compound that inhibits a wild type herpes virus which is the same strain as the mutant herpes virus.

The present invention further provides a compound for treating herpesviral infections in a human host wherein IC_{50} of the compound that inhibits a binding domain mutant herpes virus is at lease 5 times greater than IC_{50} of the compound that inhibits a wild type herpes virus which is the same strain as the mutant herpes virus.

The present invention further provides a compound for treating herpesviral infections in a human host wherein said compound inhibits the herpesvirus by interacting with the binding domain in the viral DNA polymerase.

The present invention further provides a compound for the inhibiting of herpesvirus DNA polymerases wherein serial passage of a wild type herpes virus in the presence of said

compound results in a change of the wild type HSV-1 polymerase at amino acid 823 from valine to alanine.

The present invention further provides a compound for inhibiting herpesvirus DNA polymerases wherein serial passage of a wild type herpes virus in the presence of said compound results a change of the wild type HCMV polymerase at amino acid 823 from valine to alanine and at amino acid 824 from valine to leucine.

The present invention further provides a mutant herpesvirus DNA molecule having a nucleotide sequence selected from a group consisting of SEQ.ID.NO. 1; SEQ.ID.NO. 3; SEQ.ID.NO. 5; SEQ.ID.NO. 7; SEQ.ID.NO. 9; and SEQ.ID.NO. 11.

The present invention further provides a mutant herpesvirus polymerase amino acid molecule having an amino acid sequence selected from a group consisting of SEQ.ID.NO. 2; SEQ.ID.NO. 4; SEQ.ID.NO. 6; SEQ.ID.NO. 8; SEQ.ID.NO. 10 and SEQ.ID.NO. 12.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 – examples of 4-oxo-DHQ and 4-oxo-DHTP compounds.

Figure 2 – Herpesvirus' polymerases amino acid conserved region.

Figure 3 – Recovered virus after serial passage of HSV-1 in presence of 20 μM of compound No. **17**.

Figure 4 – Comparision of Wild HSV-1 and HSV-2 herpesvirus DNA polymerase amino acid sequences alligned by amino acid homology. (Seq. No: 14-19)

Figure 5 – Mutant Herpes Virus DNA and amino acid sequence list. (Seq. No: 1-12)

Figure 6 – Wild HCMV herpesvirus DNA polymerases amino acid sequence. (Seq. No 13)

DETAILED DESCRIPTION OF THE INVENTION

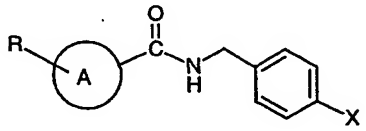
A key enzyme in the replication of all herpesviruses is the virus-coded DNA polymerase. Most of the currently available anti-herpes drugs target the viral DNA polymerase. Drugs such as Foscarnet acts by direct inhibition of the viral polymerase. These drugs are non-nucleoside inhibitors of herpesvirus DNA polymerases. Others such as the nucleoside analogs, Acyclovir, Penciclovir and Ganciclovir must first be phosphorylated to the monophosphate forms by virus encoded kinases and, further phosphorylated to triphosphate by cellular enzymes before they are active inhibitors. The triphosphate forms of these nucleoside analogs inhibit polymerases by competing with the binding of natural

triphosphates and their subsequent insertion into growing DNA strands. These drugs are known as nucleoside inhibitors of herpesvirus DNA polymerases.

One of the limitations of the currently available drugs is that they are active against only a few of the eight human herpesviruses. For example, Acyclovir and Penciclovir inhibit HSV and VZV replication but have poor activity against CMV.

In order to identify antiviral compounds that would have the potential to inhibit replication of most of the human herpesviruses, compounds are *in vitro* screened for inhibitors of herpesvirus DNA polymerase activity. Because portions of the amino acid sequence of the polymerases are highly conserved within the herpesvirus family it is possible to discover small molecules that inhibit herpesvirus polymerases but not cellular DNA polymerases. Using this biochemical approach, several new classes of compounds such as the 4-hydroxyquinoline derivatives (4-HQ), 4-oxo-dihydroquinoline derivatives (4-oxo-DHQ) and 4-oxo-dihydrothienopyridine derivatives (4-oxo-DHTP) were discovered as potent, non-nucleoside herpesvirus DNA polymerase inhibitors. *In vitro* polymerase assays and/or *in vivo* cell culture assays have demonstrated that these compounds inhibit HSV-1, HSV-2, HCMV, VZV, EBV, and HHV-8 replication.

4-Oxo-DHQ and 4-oxo-DHTP are derivatives of formula I



I

wherein ring A is a saturated or unsaturated fused double or triple heterocyclic ring having 1, 2, 3 or 4 heteroatoms selected from group consisting of oxygen, sulfur, or nitrogen; and wherein R and X are the appropriated substitutents, respectively.

Examples of 4-HQ compounds, 4-oxo-DHQ compounds and 4-oxo-DHTP compounds are illustrated in **Figure 1.**

Antiviral activity of these examples are shown in Table 1 below. As shown in Table 1, these compounds inhibit HSV-1 and HSV-2 as well or better than the current commercially available drug Acyclovir.

Table 1

Antiviral Activity of 4-oxo DHQ/4-oxo DTHP Against HSV-1 and HSV-2

	Compound IC_{50} (uM)					
virus	1	2	3	4	5	ACV
HSV-1 KOS	2.0	3.8	3.2	3.2	3.3	3.6
HSV-1 F	2.5	2.3	2.2	2.1	2.6	1.3
HSV-1 DJL	2.5	2.6	1.8	2.2	2.7	1.8
HSV-1 Patton	ND	5.3	7.7	4.3	10	9.3
HSV-2 MS	2.0	2.5	2.8	2.5	2.5	10
HSV-2 35D	ND	5.4	5.0	3.2	8.1	6.0
HSV-2 186	2.0	2.3	3.2	2.3	4.2	>10

It has also been discovered that point mutations within the HSV-1 polymerase gene that confer resistance to Acyclovir and other nucleoside analogs do not result in resistance to the 4-HQ, 4-oxo-DHQs or 4-oxo-DHTPs. Serial passage of wild type HSV-1 in the presence of 4-oxo-DHQ results in the isolation of mutants that are highly resistant (>20 fold increase in the IC_{50}) to these compounds while retaining sensitivity to nucleoside inhibitors such as Acyclovir.

In order to determine the mechanism of action of 4-HQ, 4-oxo-DHQ and 4-oxo-DHTP compounds against herpes viruses, mutants resistant to these compounds are isolated by serial passage of the virus in the presence of a 4-oxo-DHQ compound. Sequencing analysis of HSV-1 and HSV-2 strains resistant to the 4-oxo-DHQ identifies that HSV-1 (KOS strain) polymerase protein and its homologous HSV-2 have a conserved region (a binding domain), which is a critical contact point for these compounds. While amino acid numbering of the DNA polymerase may vary between strains of HSV-1 and HSV-2, this binding domain encompassing the HSV-1 (KOS) strain amino acid 823 is highly conserved in herpesviruses and can be identified by alligning the homologous amino acids of this domain as shown in Fig 2.

In HSV-1 and HSV-2 strains resistant to the 4-oxo-DHQ and similar compounds, a change of valine to an alanine at the binding domain provides full resistance.

In the HSV-1 DNA polymerase, resistance is also found when a valine changes to methionine at amino acid 823 but only when accompanied by a second amino acid change.

Isolation of HCMV resistant to 4-oxo-DHQ's is found to be very difficult. Comparison of the amino acid sequence of the HSV polymerase (Y-G-F-T-G-V-Q-H-G) and HCMV polymerase (Y-G-F-T-G-V-V-N-G) in the region of amino acid 823 (underlined amino acid) shows that there is a second valine at position 824 in the HCMV

polymerase. In vitro assay using mutant HCMV polymerases demonstrates that full resistance to the 4-oxo-DHQs requires changes at both amino acids 823 (a valine to alanine) and 824 (a valine to leucine). A HCMV polymerase gene containing V823A and V824L mutations is used in marker rescue experiments to generate a viral mutant. This mutant has an IC_{50} approximately 7-fold above that of wild-type HCMV.

The HSV-1, HSV-2 and HCMV mutants are also found to be resistant to other non-nucleoside inhibitors such as the 4-oxo-DHTP and similar compounds. However, when the binding domain mutants (e. g. HSV-1 V823A, HSV-2-MS V826A, HSV-2-186 V828A, and HCMV V823A/V824L mutants) are tested in plaque reduction assays against a series of nucleoside polymerase inhibitors and the non-nucleoside inhibitor such as Foscarnet, replication of the mutants is found to be inhibited by all of the currently marketed anti-herpes polymerase inhibitors tested.

These studies demonstrate that certain non-nucleosides like 4-HQ, 4-oxo-DHQ and 4-oxo-DHTP compounds bind to a different site on the herpes polymerase than the nucleoside inhibitors and Foscarnet. The valine at the binding domain is conserved in the DNA polymerases of six of the eight human herpesviruses and several animal herpesviruses, and appears to play a critical role in the antiviral activity of the 4-HQ, 4-oxo-DHQ and 4-oxo-DHTP compounds. (See **Figure 2**)

Since mutation at the binding domain negates these non-nucleoside inhibitors' activities, compounds could be tested against wild type polymerases and the mutant polymerases to establish the probability of similar binding. We refer to this property of compounds as interaction with the binding domain. Since compounds that interact with the binding domain have exhibited broad-spectrum activity against herpesviruses, this invention provides a method for selecting compounds to treat individuals such as immunocompromised patients who are afflicted with multple herpesvirus infections.

Definitions

The term " wild-type" refers to a gene or gene product which has the characteristics of that gene or gene product when isolated from a naturally occurring source. A wild-type gene is that which is most frequently observed in a population and is thus arbitrarily designated the "normal" or " wild-type" form of the gene.

In contrast, the term "mutant" refers to a gene or gene product which displays modifications in sequence and or functional properties (i.e., altered characteristics) when

compared to the wild-type gene or gene product. It is noted that naturally-occurring mutants can be isolated; these are identified by the fact that they have altered characteristics when compared to the wild-type gene or gene product.

IC_{50} refers to concentration of a drug that inhibits virus growth by 50%.

Wild type HSV-1 and HSV-2 strains are listed in **Figure 4.**

Wild type HCMV is listed in SEQ. ID. NO.13.

The term "Iudr" refers to antiviral drug Iododeoxyuridine.

The term "Bvdu" refers to antiviral drug Bromovinyldeoxyuridine.

The term "ACV" refers to antiviral drug Acyclovir.

The term "AraC" refers to antiviral drug Arabinosylcytidine.

The term "AraT" refers to antiviral drug Arabinosylthymine.

The term "AraA" refers to antiviral drug Arabinosyladenine.

The term "GCV" refers to antiviral drug Ganciclovir.

The term "CDV" refers to antiviral drug Cidofovir.

The term "PFA" refers to antiviral drug Foscarnet.

The term "binding domain" refers to a conserved region in herpesvirus DNA polymerases. The herpesvirus DNA polymerases have seven (7) conserved regions. The binding domain is within the thrid conserved region (see Figure 2). When the binding domain contacts with an inhibitor, at least one amino acid in the binding domain mutates and provides the resistance. In general, the binding domain is at an amino acid sequence position 818-829 of the HSV-1 DNA polymerase or the homologous region in other herpes virus DNA polymerases (see Figure 2).

The term "a binding domain mutant herpes virus" refers to a herpes virus containing a binding domain mutation.

More specifically, the binding domain in HSV-1 strains, KOS, F, DJL and Patton are at amino acid sequence position 823. The binding domain in HSV-2 MS-M1 strain is at amino acid sequence position 826. The binding domain in HSV-2 186 strain is at amino acid sequence position 828. The binding domain in HCMV AD 169 strains is at amino acid sequence position 823-824.

The term "XxxxY" refers to an amino acid sequence position xxx, a single amino acid X in wild type is changed to an amino acid Y.

For example, the term "V823A" refers to an amino acid sequence position 823, a Valine found in wild type is changed to alanine in mutant strain.

The term "V824L" refers to an amino acid sequence position 824, a Valine found in wild type is changed to Leucine in mutant strain.

The term "V826A" refers to an amino acid sequence position 826, a Valine found in wild type is change to alanine in mutant strain.

The term "V828A" refers to an amino acid sequence position 828, a Valine found in wild type is change to alanine in mutant strain.

A table of amino acids and their representative abbreviations, symbols and codons is set forth below in the following Table.

Amino acid	Abbrev.	Symbol	Codon(s)					
Alanine	Ala	A	GCA	GCC	GCG	GCU		
Cysteine	Cys	C	UGC	UGU				
Aspartic acid	Asp	D	GAC	GAU				
Glutamic acid	Glu	E	GAA	GAG				
Phenylalanine	Phe	F	UUC	UUU				
Glycine	Gly	G	GGA	GGC	GGG	GGU		
Histidine	His	H	CAC	CAU				
Isoleucine	Ile	I	AUA	AUC	AUU			
Lysine	Lys	K	AAA	AAG				
Leucine	Leu	L	UUA	UUG	CUA	CUC	CUG	CUU
Methionine	Met	M	AUG					
Asparagine	Asn	N	AAC	AAU				
Proline	Pro	P	CCA	CCC	CCG	CCU		
Glutamine	Gln	Q	CAA	CAG				
Arginine	Arg	R	AGA	AGG	CGA	CGC	CGG	CGU
Serine	Ser	S	AGC	AGU	UCA	UCC	UCG	UCU
Threonine	Thr	T	ACA	ACC	ACG	ACU		
Valine	Val	V	GUA	GUC	GUG	GUU		
Tryptophan	Trp	W	UGG					
Tyrosine	Tyr	Y	UAC	UAU				

MATERIALS AND METHODS

Cell and Viruses

African green monkey kidney cells (Vero) and human foreskin fibroblast cells (HFF) and herpes viruses can be obtained from the American Type Culture Collection (ATCC). Media is defined as Dulbecco's modified Eagle media (DMEM) containing 10% fetal bovine serum (FBS) and supplemented with antibiotics. Cells are maintained in media at 37°C in a humidified atmosphere of 5% CO^2. HSV-1 strains F, Patton and DJL, HSV-2 strains MS, 35D and 186, and HCMV strain AD169 are used in these studies. Strain DJL is a clinical isolate of HSV-1 isolated in our lab from a primary oral lesion.

Measuring IC_{50} of a Compound of Interest That Inhibits Herpes Viruses

Preparation of Virus Stocks: HSV-1 and HSV-2 stocks are grown in Vero cells. HCMV stocks are grown in HFF cells. Approximately 1 ml of media containing sufficient virus to infect approximately 0.1% to 1% of the cells (multiplicity of infection of 0.001 to 0.01 PFU/cell) is added to a T-150 cell culture flask containing a confluent monolayer of cells. The cells are incubated at 37°C for approximately 1 hour. Approximately 50 ml of media is then added to the flask and the cells are incubated at 37°C until viral cytopathic effect (cpe) is apparent in 100% of the cells. The flask is then placed at –80°C for at least 30 min. The flask containing frozen media and cells is placed in a 37°C water bath until the media is thawed. This process disrupts the cells and releases virus into the media. 1 ml aliquots of media containing virus are dispensed into tubes and stored at –80°C. These aliquots of media containing virus are referred to as virus stocks.

Titrating Virus Stocks: Aliquots of virus are thawed at 37°C and serially diluted (10 fold dilutions) in media. 0.1 ml of each dilution of virus is placed in a single well of 24-well cell culture dish containing a confluent monolayer of cells (Vero cells for HSV-1 and HSV-2, HFF cells for HCMV) and incubated at 37°C for 1 h. The virus innoculum is then removed and 1 ml of media containing 0.8% carboxymethylcellulose (CMC) is added to each well of the dish. The dish is incubated at 37°C for approximately 2-3 days (HSV-1 and HSV-2) or 6-9 days (HCMV) to allow sufficient growth of virus to form plaques in the cell monolayer. Plaques can be observed and counted microscopically or by staining the cells with 0.1% crystal violet in 20% ethanol. The virus titer which is expressed as plaque forming units (PFU) per ml is obtained by counting the plaques in a well and correcting for the dilution of the viral innoculum.

Plaque Reduction Assays: Antiviral activity of compounds against herpesviruses such as HSV-1, HSV-2, or HCMV can be measured using plaque reduction assays. 0.1 ml of media containing approximately 50 PFU of virus is added to each well of a 24-well cell culture dish containing a confluent monolayer of cells (Vero cells for HSV-1 and HSV-2, HFF cells for HCMV). Compounds are dissolved in 100% DMSO and diluted in 100% DMSO as 200x stocks of the desired final drug concentration. Typically 5-6 two-fold dilutions are prepared for each compound. Dilutions of compounds are then added to media containing 0.8% CMC resulting in a final 1x drug concentration. After the virus-infected cells have incubated for 1 h at 37°C, the virus innoculum is removed and 1 ml of media containing 0.8% CMC and the various concentrations of compound is added to each well of the dish.

The dish is incubated at 37°C for approximately 2-3 days (HSV-1 and HSV-2) or 6-9 days (HCMV) to allow sufficient growth of virus to form plaques in the cell monolayer. Plaques can be observed and counted microscopically or by staining the cells with 0.1% crystal violet in 20% ethanol. Virus inhibition is determined for each drug concentration by comparing the number of plaques in drug-containing wells to control wells that did not contain drug. Antiviral activity of a compound is expressed as the concentration of compound predicted to reduce the number of plaques in a well by 50% (IC_{50}). The IC_{50} values are calculated by plotting the per cent inhibition vs. concentration of compound using EXCEL software for linear regression.

Selection of 4-oxo-DHQ resistant HSV-1 and HSV-2

Vero cells are plated out at a density of $3.5x10^5$ cells per well in a six well tissue culture plate. Cells are infected with HSV-1 KOS at a multiplicity of infection (moi) of 0.1 pfu/cell and 1 h post infection the cells are overlayed with 3 ml media containing 20 uM of a 4-oxo-DHQ. Cultures are incubated for 20 h at 37°C, freeze/thawed to release cell-associated virus, and 0.1 ml of culture is used to infect a new monolayer of Vero cells (one passage). Serial passage is repeated seven times in the presence of 20 uM drug. Virus isolates are then plaque purified three times prior to preparation of stocks. Virus recovered from each passage in the presence of compound No. 17 is shown in **Figure 3**. 4-oxo-DHQ resistant HSV-1 and HSV-2 may also be selected by the marker transfer method described below using wild-type HSV DNA and the corresponding mutant HSV polymerase gene.

Marker Transfer of a HCMV Mutation

A plasmid containing the wild-type HCMV polymerase gene is modified to contain the V823A or V823A and V824L mutations using a site-directed mutagenesis Kit (Stratagene Corp.) and following the manufactures's protocol. HFF cells are plated into T25 tissue culture flasks to achieve 80% confluency at the time of the transfection. Wild type HCMV AD169 DNA and plasmid DNA containing the mutant HCMV polymerase gene are mixed at a ratio of 1:2 (2ug of viral DNA to 4 ug of plasmid DNA). DNA's are transfected using superfect transfection reagent according to methods recommended by the manufacturer (Quiagen Inc.). Cells are harvested five days posttransfection, freeze-thawed to release virus and half of the sample is used to infect HFF cell monolayers. Cells are overlayed with media containing 20 uM 4-oxo-DHQ compound **2** (see Figure 1). Serial

passage is repeated seven times in the presence of 20 uM compound **2** and virus isolates are then plaque purified three times prior to preparation of viral stock.

Isolation of HSV and HCMV viral DNA

HSV DNA is purified from the cytoplasm of infected Vero cells. Vero cells (50 % confluent) are infected at an multiplicity of 0.01 PFU/cell. At 3-5 days postinfection infected cells (100% cpe) are harvested by centrifugation at 1000 rpm in a Beckman GS-6R centrifuge. The pelleted cells are resuspended in TE buffer and placed on ice for 15 minutes. NP-40 is then added to a final concentration of 0.2% and incubated on ice for a further 15 minutes. The cells are centrifuged at 2000 rpm for 10 minutes in a Beckman GS-6R centrifuge. The supernatant is removed and EDTA is added to a final concentration of 20 mM followed by the addition of SDS to a final concentration of 0.3% and proteinase K to a concentration of 50 ug/ml then incubated at 45C for 2 hours. HCMV DNA is isolated by infecting HFF cells (25% confluency) with HCMV at an multiplicity of 0.1 PFU/cell. Cells and media are harvested 5-7 days postinfection (100% cpe) and subjected to low speed centrifugation to remove intact cells and cell debris followed by a high speed spin to pellet virus particles (2500 rpm's in a Beckman SW28 rotor for 1 hour). Following incubation of the HSV and HCMV samples, 1.5 volumes of saturated NaI is added to the digested extract and the refractive index is adjusted to 1.434 –1.435. Ethidium bromide is added to a final concentration of 50 ug/ml. The samples are loaded into a VTI 50centrifuge tube and spun for 24 hours at 45,000 rpm. The DNA band is harvested extracted three times with n-butanol, then dialyzed against TE buffer followed by a dialysis against 95% ethanol and a final dialysis against TE buffer.

DNA Sequencing

HSV-1, HSV-2 or HCMV viral DNA's are sequenced directly using an ABI377 fluorescence sequencer (Perkin Elmer Applied Biosystems, Foster City, CA) and the ABI BigDye PRISMTM dRhodamine Terminator Cycle Sequencing Ready Reaction Kit with AmpliTaq FSTM DNA polymerase (PE Applied Biosystems). Each cycle sequencing reaction contained about 1.0 ug of purified viral DNA. Cycle-sequencing is performed using an initial denaturation at 98°C for 1 min, followed by 50 cycles: 98°C for 30 sec, annealing at 50°C for 30 sec, and extension at 60°C for 4 min. Temperature cycles and times are controlled by a Perkin-Elmer 9700 thermocycler. Extension products are

purified using CentriflexTM gel filtration cartridges (Edge BioSystems, Gaithersburg, MD). Each reaction product is loaded by pipette onto the column, which is then centrifuged in a swinging bucket centrifuge (Sorvall model RT6000B table top centrifuge) at 750 x g for 1.5 min at room temperature. Column-purified samples are dried under vacuum for about 40 min and then dissolved in 4 ul of a DNA loading solution (83% deionized formamide, 8.3 mM EDTA, and 1.6 mg/ml Blue Dextran). The samples are then heated to 90°C for two min, and held at 4°C until loading. 1.5 ul of each sample is loaded into a single well of the ABI377 sequencer. Sequence chromatogram data files from the ABI377 are analyzed with the computer program Sequencher (Gene Codes, Ann Arbor, MI), for assembly of sequence fragments and correction of ambiguous base calls. Generally sequence reads of 600-700 bp are obtained. Potential sequencing errors are minimized by obtaining sequence information from both DNA strands and by re-sequencing difficult areas using primers at different locations until all sequencing ambiguities are removed.

The entire coding region of the polymerase genes from both the parent strains and the resistant viruses are sequenced. The DNA sequencing is done using viral DNA as the template thus avoiding cloning of the polymerase genes. The amino acid sequence of the DNA polymerases of HSV-1 KOS, F, Patton and DJL and HSV-2 MS and 186 are compared in **Figure 4**. Amino acids that are identical for the six polymerases are shaded in black while regions where amino acid differences are found are shaded in gray. The amino acid sequence of the four HSV-1 polymerases are essentially identical with only a few minor changes noted between the different HSV-1 strains. The majority of amino acid changes are found when the sequences of the HSV-1 and HSV-2 polymerases are compared.

Isolation and Characterization of HSV-1 and HSV-2 Mutants That Are Resistant To the 4-oxo-DHQ's and 4-oxo-DHTP Compounds

A panel of viruses consisting of four strains of HSV-1 (KOS, F, DJL, Patton) and three strains of HSV-2 (MS, 35D, 186) are tested in a plaque reduction assay against four different 4-oxo-DHQ compounds (# **1, 2, 4, 5** as shown in Figure 1), and one 4-oxo-DHTP compound (# **3** as shown in Figure 1) and against Acyclovir. The six drugs inhibited replication of the seven virus strains with IC_{50} values ranging from 2-10 μM (Table 1). In order to select for 4-oxo-DHQ resistant mutants, HSV-1 strains KOS, F, and DJL along with HSV-2 strains 186 and MS are serially passaged in the presence of 20 uM compound

1. Following the seventh passage, 4-oxo-DHQ resistant virus from each strain are plaque purified three times and high-titer stocks are made. All of the resistant HSV mutants grew to high titers in Vero cells, indicating that the mutations in the resistant isolates did not significantly impair their growth. The mutants selected with 4-oxo-DHQ compound 1 exhibited >10 fold increase in IC_{50} when tested in a plaque reduction assay against 4-oxo-DHQ compound 1 Data are shown in Table 2.

Table 2

4-oxo-DHQ Resistant Virus of HSV-1 and HSV-2

Virus Mutants	Compound 1 IC_{50} (uM)	Amino Acid Change in HSV DNA Polymerase
HSV-1 Kos-M1	>20	- V823A
HSV-1 F-M1	>20	- V823A
HSV-1 DJL-M1	>20	-V823A
HSV-2 MS-M1	>20	- V826A
HSV-2 186-M1	>20	- V828A

*HSV-1 and HSV-2 isolates grown in the presence of 4-oxo-DHQ select for resistant virus.

DNA sequence analysis of the 4-oxo-DHQ resistant mutants (HSV-1 KOS-M1, HSV-1 F-M1, HSV-1 DJL-M1, HSV-2 186-M1, HSV-2 MS-M1) demonstrated that all five mutants contained a single point mutation of T to C at the binding domain resulting in a Valine to Alanine amino acid change.

Isolation and Characterization of A HCMV Mutant That Is Resistant to The 4-oxo-DHQ's and 4-oxo-DHTP Compounds

In order to select for a 4-oxo-DHQ HCMV resistant mutant, virus (strain AD169) is serially passaged in the presence of 20 uM a 4-oxo-DHQ. Although we could readily select for HSV mutants using this procedure we failed to isolate an HCMV mutant, even when the virus is passaged at low drug concentrations (<5 uM). Comparison of the amino acid sequence of the HSV polymerase, Y-G-F-T-G-V-Q-H-G, and HCMV polymerase, Y-G-F-T-G-V-V-N-G, in the region of amino acid 823 (underlined amino acid) showed that there is a second valine at position 824 in the HCMV polymerase. In order to determine if both valines need to be changed in order to confer resistance to the 4-oxo-DHQ's, *in vitro* polymerase assays are done using mutant HCMV polymerases containing either V823A or V823A plus V824L (Table 3).

Table 3

HCMV Mutant Polymerase Exhibits Resistance to 4-oxo-DHQ*

Polymerase	Compound 1 IC_{50} (uM)
HCMV (wild)	4.6
HCMV V823A	17.2
HCMV V823A/V824L	42.9

*Generation of the valine to alanine at amino acid 823 of HCMV results in a 3.5-fold increase in resistance.

*Mutation of the amino acid from valine to alanine and amino acid 824 from valine to leucine results in an 9-fold increase in resistance, relative to wild type.

The V823A alone resulted in a 3.5-fold increase in the IC_{50} while the polymerase with the double amino acid change had nearly 10-fold increase in the IC_{50}. In order to isolate an HCMV resistant mutant marker rescue experiments are done. Plasmids containing the mutant polymerase genes are transfected into HFF cells along with wild type HCMV AD169 DNA. The resulting virus is then serially passaged in the presence of 20 uM compound **1** (see figure 1). A 4-oxo-DHQ resistant virus is isolated from marker rescue studies done with the HCMV polymerase gene containing mutations that result in the V823A, V824L amino acid changes, but not with the gene containing V823A change alone. The mutant selected with compound **1** (HCMV AD169-M1) exhibited ~7-fold increase in IC_{50} when tested in a plaque reduction assay compared to Ganciclovir and cidofovir which has a $\leq$ 2-fold change in sensitivity (Table 4).

Table 4

Plaque reduction assay of 4-oxo-DHQ resistant HCMV*

Drug	HCMV AD169 IC_{50} (μM)	HCMV AD169 – M1 IC_{50} (μM)
Compound 1	0.7	4.7
Ganciclovir	0.9	1.0
Cidofovir	0.3	0.6

*Recombination of wild-type HCMV with a polymerase gene containing the valine to alanine at amino acid 823 and the valine to leucine at amino acid 824 allowed for selection of resistant virus with about 7-fold less sensitivity to compound 1.

*Sensitivity of resistant HCMV virus to Ganciclovir and Cidofovir verifies that the 4-oxo-DHQ's mechanism for inhibiting the polymerase protein is unique

The entire coding region of the HCMV polymerase genes from both the parent strain and the resistant virus are sequenced. The DNA sequencing is again done using viral DNA as the template thus avoiding cloning of the polymerase genes. Comparison of the DNA sequence of the two polymerase genes demonstrated that the resistant mutant contained two point mutations that resulted in the predicted V823A, V824L amino acid changes. As with the HSV resistant viruses these results demonstrate the critical role of the region encompassing amino acid 823 for inhibition of polymerase activity by these compounds.

Antiviral Activity of Nucleoside and Non-Nucleoside Polymerase Inhibitors Against 4-oxo-DHQ Resistant Mutants

In order to determine if the 4-HQ binding domain mutations alter the sensitivity of the HSV-1, HSV-2 and HCMV mutants to both non-nucleoside (4-oxo-DHQ's) and nucleoside inhibitors (e.g Acyclovir and ganciclovir) several of the mutants are tested in plaque reduction assays against a series of non-nucleoside compounds including Foscarnet (PFA), 4-HQ's 4-oxo-DHQ's and 4-oxo-DHTP's (Table 5). The mutants are also tested against a series of nucleoside inhibitors including acyclovir and ganciclovir (Table 5). The activity of these compounds against the mutants is compared to their activity against the wild type strains that are used to isolate the HSV and HCMV mutants. When tested against a number of 4-HQ's, 4-oxo-DHQ's and 4-oxo-DHTP's and other related classes of compounds all of the drugs are found to inhibit the wild type virus with IC_{50} values ranging from <0.1 uM to 30 uM. When these drugs are tested against the resistant viruses they are found to have IC_{50} values 5 to 10 fold higher then the parent virus. There is little if any difference in the IC_{50} values of the nucleoside compounds and the non-nucleoside PFA between the wild type and mutant HSV-1, HSV-2, and HCMV viruses. These results demonstrate that the amino acid change in the binding domain (V823A in the HSV-1 polymerase, V826A in the HSV2-MS polymerase, V828A in the HSV2-186 polymerase, and the V823A/V824L changes in the HCMV polymerase) resulted in resistance to the 4-oxo-DHQ's and 4-oxo-DHTP's, which provides further evidence that these classes of compounds share an affinity for a region we refer to as the binding domain. In contrast, these amino acid changes did not alter the activity of these viruses to other classes of polymerase inhibitors.

Table 5

Antiviral activity of nucleoside and non-nucleoside polymerase inhibitors against HSV-1, HSV-2, and HCMV Isolates selected for 4-oxo-DHQ resistance*

	Plaque Reduction Assay – IC_{50} (μM)					
Drug	HSV-2 MS	HSV-2 MS-M1	HSV-1 KOS	HSV-1 KOS-M1	HCMV AD169	HCMV AD169-M1
6	28.8	>50	24.6	>50	5.1	>16
7	8.8	27.9	6.5	>50	0.3	3.4
8	2.3	>50	5.1	>50	<0.1	1.1
9	0.9	48.7	1.9	>50	<0.1	3.1
10	29.2	>50	15.8	>50	1.1	>16
11	3.0	>50	3.1	>50	0.7	3.9
12	0.4	12.5	1.3	>50	0.2	1.1
13	5.3	>50	5.5	<25	2.7	>16
14	1.6	>50	28.4	>50	0.9	18.4
2	1.3	>50	3.3	>50	0.4	4.0
4	2.1	28.4	4.2	>50	0.6	2.1
3	0.8	>50	4.0	>50	1.5	6.2
15	5.9	>50	>50	>50	0.7	7.7
Iudr	5.0	6.1	1.1	0.8	ND	ND
Bvdu	5.8	5.9	2.1	0.1	ND	ND
ACV	2.4	2.8	3.9	4.4	ND	ND
AraC	0.2	0.1	0.2	0.2	ND	ND
AraT	6.6	3.6	11.6	3.6	ND	ND
AraA	10.6	18.2	26.1	27.2	ND	ND
GCVir	ND	ND	ND	ND	0.8	0.8
CDV	ND	ND	ND	ND	0.4	0.3
PFA	ND	ND	ND	ND	38	<20

*HSV-2 MS, HSV-1 KOS, HCMV AD169: wild type strains
*HSV-2 MS-M1, HSV-1 KOS-M1, HCMV AD169-M1: mutants selected for 4-oxo-DHQ resistance
*ND – Not Done.

Antiviral compounds identified by the present invention can conveniently be administered in a pharmaceutical composition containing the compound in combination with a suitable excipient, the composition being useful in combating viral infections. Pharmaceutical compositions containing a compound appropriate for antiviral use are prepared by methods and contain excipients which are well known in the art. A generally recognized compendium of such methods and ingredients is Remington's Pharmaceutical Sciences by E.W. Martin (Mark Publ. Co., 15th Ed., 1975).

Antiviral compounds identified by the present invention and their compositions can be administered parenterally (for example, by intravenous, intraperitoneal or intramuscular

injection), topically, orally, or rectally, depending on whether the preparation is used to treat internal or external viral infections.

For oral therapeutic administration, the active compound may be combined with one or more excipients and used in the form of ingestible tablets, buccal tablets, troches, capsules, elixirs, suspensions, syrups, wafers, and the like. Such compositions and preparations should contain at least 0.1% of active compound. The percentage of the compositions and preparations may, of course, be varied and may conveniently be between about 2 to about 60% of the weight of a given unit dosage form. The amount of active compound in such therapeutically useful compositions is such that an effective dosage level will be obtained.

The tablets, troches, pills, capsules, and the like may also contain the following: binders such as gum tragacanth, acacia, corn starch or gelatin; excipients such as dicalcium phosphate; a disintegrating agent such as corn starch, potato starch, alginic acid and the like; a lubricant such as magnesium stearate; and a sweetening agent such as sucrose, fructose, lactose or aspartame or a flavoring agent such as peppermint, oil of wintergreen, or cherry flavoring may be added. When the unit dosage form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier, such as a vegetable oil or a polyethylene glycol. Various other materials may be present as coatings or to otherwise modify the physical form of the solid unit dosage form. For instance, tablets, pills, or capsules may be coated with gelatin, wax, shellac or sugar and the like. A syrup or elixir may contain the active compound, sucrose or fructose as a sweetening agent, methyl and propylparabens as preservatives, a dye and flavoring such as cherry or orange flavor. Of course, any material used in preparing any unit dosage form should be pharmaceutically acceptable and substantially non-toxic in the amounts employed. In addition, the active compound may be incorporated into sustained-release preparations and devices.

Antiviral compounds identified by the present invention and their compositions can also be administered intravenously or intraperitoneally by infusion or injection. Solutions of the active compound or its salts can be prepared in water, optionally mixed with a nontoxic surfactant. Dispersions can also be prepared in glycerol, liquid polyethylene glycols, triacetin, and mixtures thereof and in oils. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms.

Pharmaceutical dosage forms suitable for injection or infusion can include sterile aqueous solutions or dispersions or sterile powders comprising the active ingredient which

are adapted for the extemporaneous preparation of sterile injectable or infusible solutions or dispersions, optionally encapsulated in liposomes. In all cases, the ultimate dosage form should be sterile, fluid and stable under the conditions of manufacture and storage. The liquid carrier or vehicle can be a solvent or liquid dispersion medium comprising, for example, water, ethanol, a polyol (for example, glycerol, propylene glycol, liquid polyethylene glycols, and the like), vegetable oils, nontoxic glyceryl esters, and suitable mixtures thereof. The proper fluidity can be maintained, for example, by the formation of liposomes, by the maintenance of the required particle size in the case of dispersions or by the use of surfactants. The prevention of the action of microorganisms can be brought about by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars, buffers or sodium chloride. Prolonged absorption of the injectable compositions can be brought about by the use in the compositions of agents delaying absorption, for example, aluminum monostearate and gelatin.

Sterile injectable solutions can be prepared by incorporating the active compound in the required amount in the appropriate solvent with various of the other ingredients enumerated above, as required, followed by filter sterilization. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum drying and the freeze drying techniques, which yield a powder of the active ingredient plus any additional desired ingredient present in the previously sterile-filtered solutions.

For topical administration, the present compounds may be applied in pure form, i.e., when they are liquids. However, it will generally be desirable to administer them to the skin as compositions or formulations, in combination with a dermatologically acceptable carrier, which may be a solid or a liquid.

Useful solid carriers include finely divided solids such as talc, clay, microcrystalline cellulose, silica, alumina and the like. Useful liquid carriers include water, alcohols or glycols or water-alcohol/glycol blends, in which the present compounds can be dissolved or dispersed at effective levels, optionally with the aid of non-toxic surfactants. Adjuvants such as fragrances and additional antimicrobial agents can be added to optimize the properties for a given use. The resultant liquid compositions can be applied from absorbent pads, used to impregnate bandages and other dressings, or sprayed onto the affected area using pump-type or aerosol sprayers. Thickeners such as synthetic polymers, fatty acids,

fatty acid salts and esters, fatty alcohols, modified celluloses or modified mineral materials can also be employed with liquid carriers to form spreadable pastes, gels, ointments, soaps, and the like, for application directly to the skin of the user.

Examples of useful dermatological compositions which can be used to deliver the compounds of formula I to the skin are known to the art; for example, see Jacquet et al. (U.S. Pat. No. 4,608,392), Geria (U.S. Pat. No. 4,992,478), Smith et al. (U.S. Pat. No. 4,559,157) and Wortzman (U.S. Pat. No. 4,820,508).

Useful dosages of the compounds of formula I can be determined by comparing their *in vitro* activity, and *in vivo* activity in animal models. Methods for the extrapolation of effective dosages in mice, and other animals, to humans are known to the art; for example, see U.S. Pat. No. 4,938,949.

The compound is conveniently administered in unit dosage form; for example, containing 5 to 1000 mg, conveniently 10 to 750 mg, most conveniently, 50 to 500 mg of active ingredient per unit dosage form. The desired dose may conveniently be presented in a single dose or as divided doses administered at appropriate intervals, for example, as two, three, four or more sub-doses per day. The sub-dose itself may be further divided, e.g., into a number of discrete loosely spaced administrations; such as multiple inhalations from an insufflator or by application of a plurality of drops into the eye.

For internal infections, the compositions can be administered orally or parenterally at dose levels, calculated as the free base, of about 0.1 to 300 mg/kg, preferably 1.0 to 30 mg/kg of mammal body weight, and can be used in man in a unit dosage form, administered one to four times daily in the amount of 1 to 1000 mg per unit dose.

For parenteral administration or for administration as drops, as for eye infections, the compounds are presented in aqueous solution in a concentration of from about 0.1 to about 10%, more preferably about 0.1 to about 7%. The solution may contain other ingredients, such as emulsifiers, antioxidants or buffers.

Generally, the concentration of the compound(s) of formula I in a liquid composition, such as a lotion, will be from about 0.1-25 wt-%, preferably from about 0.5-10 wt-%. The concentration in a semi-solid or solid composition such as a gel or a powder will be about 0.1-5 wt-%, preferably about 0.5-2.5 wt-%.

The exact regimen for administration of the compounds and compositions disclosed herein will necessarily be dependent upon the needs of the individual subject being treated, the type of treatment and, of course, the judgment of the attending practitioner.

The antiviral activity of a compound of the invention can be determined using pharmacological models which are well known to the art, or using Test A described below.

The compounds of formula (I) and pharmaceutically acceptable salts thereof are useful as antiviral agents. Thus, they are useful to combat viral infections in animals, including man. The compounds are generally active against herpes viruses, and are particularly useful against the varicella zoster virus, the Epstein-Barr virus, the herpes simplex virus, the human herpes virus type 8 (HHV-8) and the cytomegalovirus (CMV).

CLAIMS

We claim:

1. A method of selecting compounds that inhibit herpes viruses comprising:

a) measuring IC_{50} of a compound of interest that inhibits a wild type herpes virus,

b) measuring IC_{50} of the same compound that inhibits a binding domain mutant herpes virus which is the same strain as the wild type herpes virus,

c) comparing IC_{50} of step a with IC_{50} of step b; and

d) selecting the compound of interest wherein the IC_{50} of step b is at least 3 times greater than the IC_{50} of step a.

2. A method of selecting compounds that inhibit herpes viruses comprising:

a) measuring IC_{50} of a compound of interest that inhibits a binding domain mutant herpes virus,

b) measuring IC_{50} of the same compound that inhibits a wild type herpes virus which is the same strain as the mutant herpes virus,

c) comparing IC_{50} of step a with IC_{50} of step b; and

d) selecting the compound of interest wherein the IC_{50} of step a is at least 3 times greater than the IC_{50} of step b.

3. The method of claim 1 or 2 wherein the herpes virus is HSV-1, HSV-2, HCMV, VZV, EBV, or HHV-8.

4. A method of selecting compounds that inhibit herpes viruses comprising:

a) measuring IC_{50} of a compound of interest that inhibits a wild type HSV-1,

b) measuring IC_{50} of the same compound that inhibits a binding domain mutant HSV-1 which is the same strain as the wild type herpes virus,

c) comparing IC_{50} of step a with IC_{50} of step b; and

d) selecting the compound of interest wherein the IC_{50} of step b is at least 3 times greater than the IC_{50} of step a.

5. A method of selecting compounds that inhibit herpes viruses comprising:

a) measuring IC_{50} of a compound of interest that inhibits a binding domain mutant HSV-1,

b) measuring IC_{50} of the same compound that inhibits a wild type herpes virus which is the same strain as the mutant HSV-1,

c) comparing IC_{50} of step a with IC_{50} of step b; and

d) selecting the compound of interest wherein the IC_{50} of step a is at least 3 times greater than the IC_{50} of step b.

6. The method of claim 4 or 5 wherein HSV-1 is HSV-1 KOS, HSV-1 F, HSV-1 DJL or HSV-1 Patton.

7. The method of claim 5 or 6 wherein the mutation of a wild type herpes virus to mutant herpes virus is at amino acid 823 from valine to alanine.

8. A method of selecting compounds that inhibit herpes viruses comprising:

a) measuring IC_{50} of a compound of interest that inhibits a wild type HSV-2,

b) measuring IC_{50} of the same compound that inhibits a binding domain mutant HSV-2 which is the same strain as the wild type herpes virus,

c) comparing IC_{50} of step a with IC_{50} of step b; and

d) selecting the compound of interest wherein the IC_{50} of step b is at least 3 times greater than the IC_{50} of step a.

9. A method of selecting compounds that inhibit herpes viruses comprising:

a) measuring IC_{50} of a compound of interest that inhibits a binding domain mutant HSV-2,

b) measuring IC_{50} of the same compound that inhibits a wild type herpes virus which is the same strain as the mutant HSV-2,

c) comparing IC_{50} of step a with IC_{50} of step b; and

d) selecting the compound of interest wherein the IC_{50} of step a is at least 3 times greater than the IC_{50} of step b.

10. The method of claim 8 or 9 wherein HSV-2 is HSV-2 MS, HSV-2 35D, or HSV-2 186.

11. A method of selecting compounds that inhibit herpes viruses comprising:

a) measuring IC_{50} of a compound of interest that inhibits a wild type HCMV,

b) measuring IC_{50} of the same compound that inhibits a binding domain mutant HCMV which is the same strain as the wild type herpes virus,

c) comparing IC_{50} of step a with IC_{50} of step b; and

d) selecting the compound of interest wherein the IC_{50} of step b is at least 3 times greater than the IC_{50} of step a.

12. A method of selecting compounds that inhibit herpes viruses comprising:

a) measuring IC_{50} of a compound of interest that inhibits a binding domain mutant HCMV,

b) measuring IC_{50} of the same compound that inhibits a wild type herpes virus which is the same strain of the mutant HCMV,

c) comparing IC_{50} of step a with IC_{50} of step b; and

d) selecting the compound of interest wherein the IC_{50} of step a is at least 3 times greater than the IC_{50} of step b.

13. The method of claim 8 or 9 wherein HCMV is AD169.

14. The methods of claims 1, 4, 8, or 11 wherein IC_{50} of step b is at least 5 times greater than the IC_{50} of step a.

15. The methods of claims 2, 5, 9, or 12 wherein IC_{50} of step a is at least 5 times greater than the IC_{50} of step b.

16. A use of compounds for manufacturing of medicinals for selectively treating diseases caused by herpes viruses in a human host comprising administering a compound to a human in need of such treatment wherein said compound inhibits herpes viruses by interaction with the binding domain in the viral DNA polymerase.

17. A use of compounds for manufacturing of medicinals for selectively inhibiting herpes viruses in a human host comprising administering a compound to a human in need of such treatment wherein IC_{50} of the compound that inhibits a binding domain

mutant herpes virus is at lease 3 times greater than IC_{50} of the compound that inhibits a wild type herpes virus which is the same strain as the mutant herpes virus.

18. The use of claim 17 wherein IC_{50} of the compound that inhibits a binding domain mutant herpes virus is at lease 5 times greater than IC_{50} of the compound that inhibits a wild type herpes virus which is the same strain as the mutant herpes viruse.

19. The use of claim 17 wherein herpes viruses is HSV-1, HSV-2, HCMV, VZV, EBV, or HHV-8.

20. A use of compounds for manufacturing of medicinals for treating herpesviral infections in a human host wherein IC_{50} of the compound that inhibits a binding domain mutant herpes virus is at lease 5 times greater than IC_{50} of the compound that inhibits a wild type herpes virus which is the same strain as the mutant herpes virus.

21. A use of compounds for manufacturing of medicinals for treating herpesviral infections in a human host wherein said compound inhibits the herpesvirus by interacting with the binding domain in the viral DNA polymerase.

22. The herpesviral infection of claim 20 or 21 which is HSV-1, HSV-2, HCMV, VZV, EBV, or HHV-8 infection.

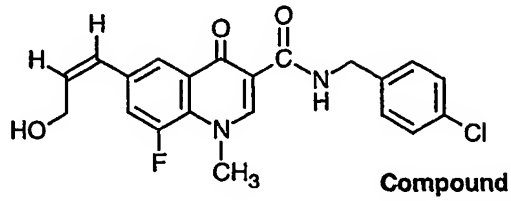
23. A compound for the inhibiting of herpesvirus DNA polymerases wherein passage of a wild type herpes virus in the presence of said compound results a change of the wild type HSV-1 polymerases at amino acid 823 from valine to alanine.

24. A compound for inhibiting herpesvirus DNA polymerases wherein passage of a wild type herpes virus in the presence of said compound results in a change of the wild type HCMV polymerases at amino acid 823 from valine to alanine and at amino acid 824 from valine to leuline.

25. A mutant herpesvirus DNA molecule having a nucleotide sequence selected from a group consisting of SEQ.ID.NO. 1; SEQ.ID.NO. 3; SEQ.ID.NO. 5; SEQ.ID.NO. 7; SEQ.ID.NO. 9; and SEQ.ID.NO. 11.

26. A mutant herpesvirus polymerase amino acid molecule having an amino acid sequence selected from a group consisting of SEQ.ID.NO. 2; SEQ.ID.NO. 4; SEQ.ID.NO. 6; SEQ.ID.NO. 8; SEQ.ID.NO. 10 and SEQ.ID.NO. 12.

Figure 1 **4-HQ, 4-oxo-DHQ and 4-oxo-DHTP antiviral compounds**



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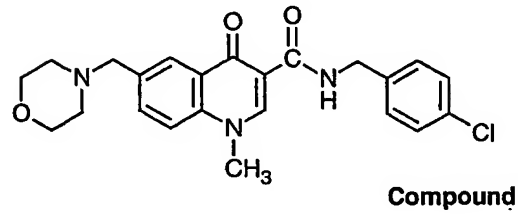

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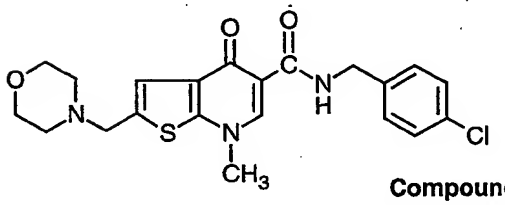

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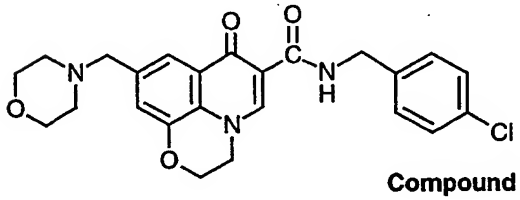

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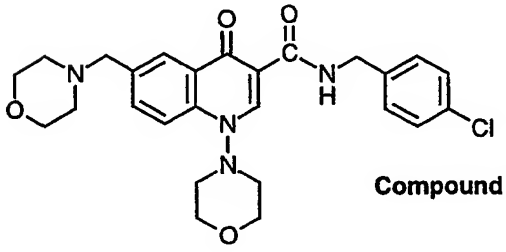
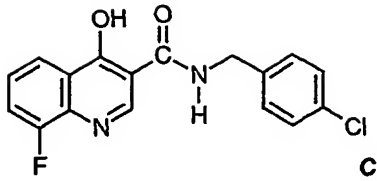
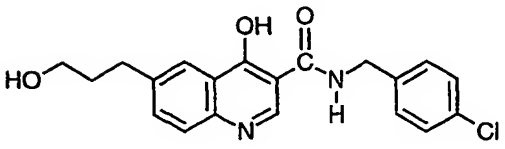


Compound No. 5

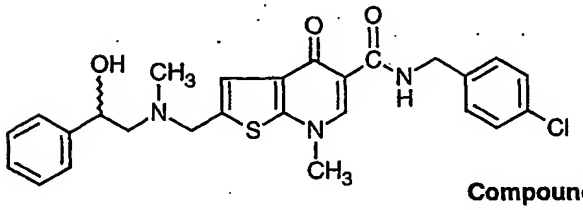
(Figure 1 continue)



Compound No. 6



Compound No. 7



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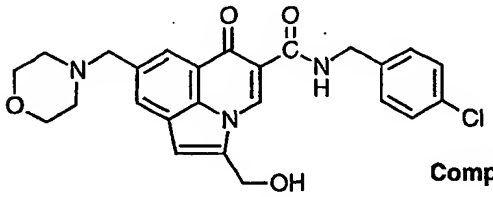

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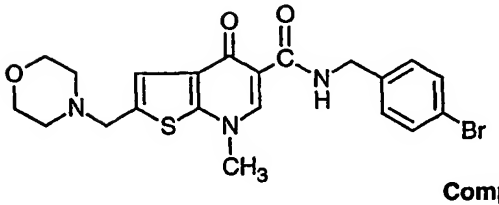
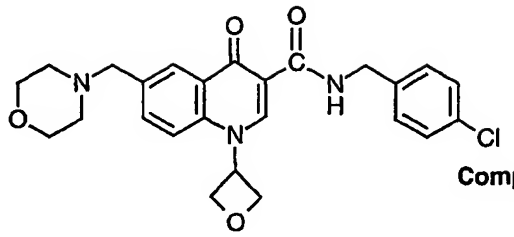
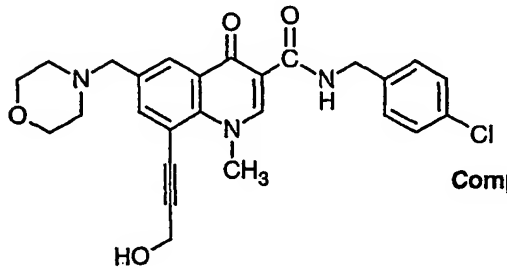


Compound No. 10

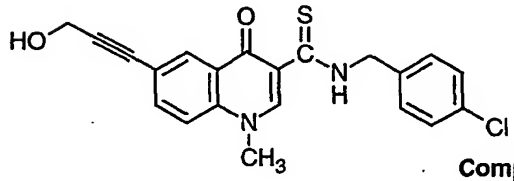
(Figure 1 continue)



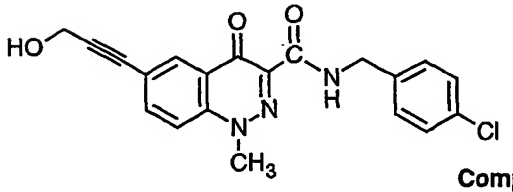
Compound No. 11



Compound No. 12

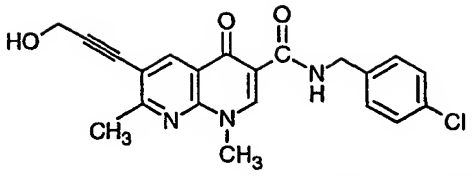


Compound No. 13

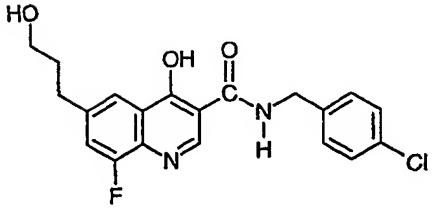


Compound No. 14

(Figure 1 continue)

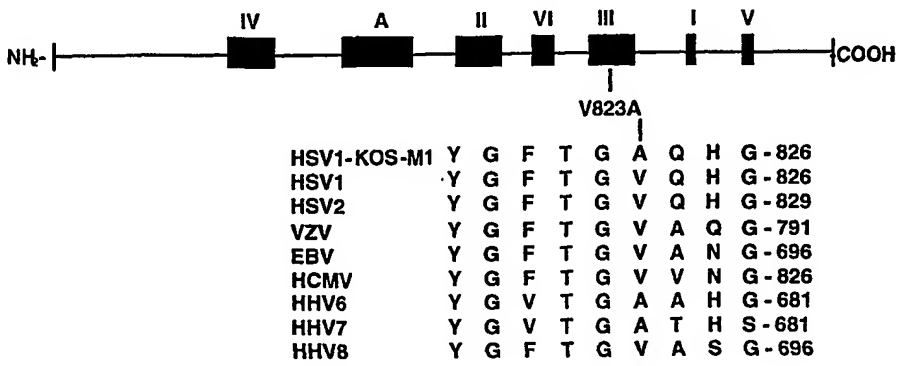


Compound No.15



Compound 17

Figure 2. The HSV1 (KOS Strain) DNA Polymerase Amino Acid 823 is Critical for Resistance to 4-Hydroxyquinolines and Related Compounds



Schematic of HSV1 polymerase illustrating the conserved regions A and I-VI found in class 2 polymerases. Also shown are the amino acid sequence for the highly conserved herpesvirus domain in region III which surrounds the HSV1 amino acid 823.

5

Figure 3 Serial Passage of HSV-1 in Presence of 20 μM compound 17

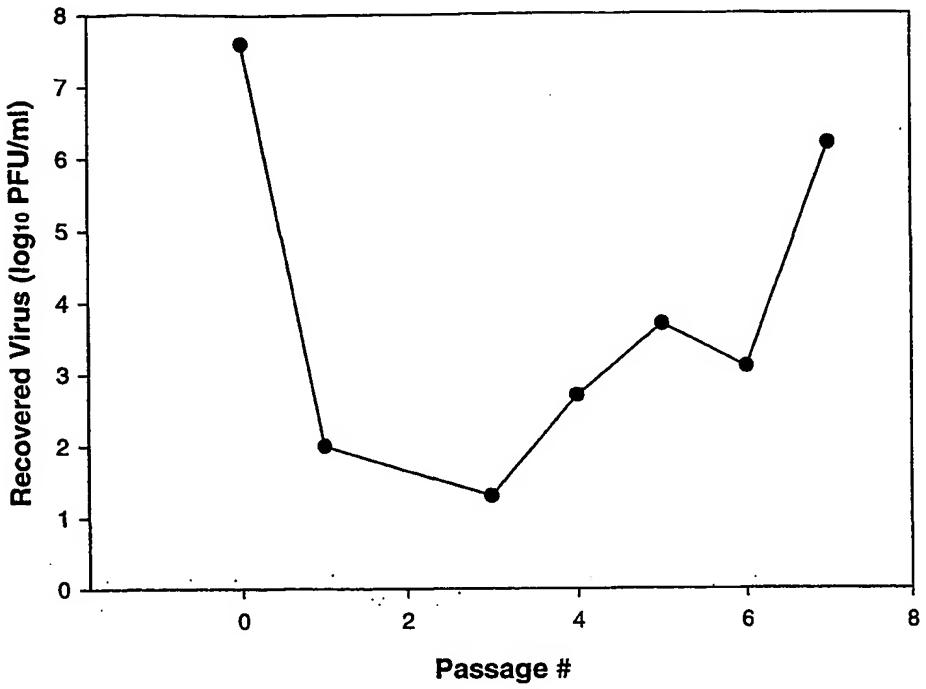


Figure 4 Comparison of Wild type HSV-1 and HSV-2 DNA Polymerases Amino Acid Sequences Alligned by Amino Acid Homology*

```
HSV2-MS       MFCAAGGPTS PGGKSAARAA SGFFAPHNPR GATQTAPPPC RRQNFYNPHL -50
HSV2-186      MFCAAGGPAS PGGKSAARAA SGFFAPHNPR GATQTAPPPC RRQNFYNPHL -50
HSV1-Kos      MFSGGGGPLS PGGKSAARAA SGFFAPAGPR GAGR.GPPPC LRQNFYNPYL -49
HSV1-Patton   MFSGGGGPLS PGGKSAARAA SGFFAPAGPR GAGR.GPPPC LRQNFYNPYL -49
HSV1-DJL      MFSGGGGPLS PGGKSAARAA SGFFAPAGPR GAGR.GPPPC LRQNFYNPYL -49
HSV1-F        MFSGGGGPLS PGGKSAARAA SGFFAPAGPR GAGR.GPPPC LRQNFYNPYL -49

HSV2-MS       AQTGTQPKAP GPAQRHTYYS ECDEFRFIAP RSLDEDAPAE QRTGVHDGRL -100
HSV2-186      AQTGTQPKAP GPAQRHTYYS ECDEFRFIAP RSLDEDAPAE QRTGVHDGRL -100
HSV1-Kos      APVGTQQKPT GPTQRHTYYS ECDEFRFIAP RVLDEDAPPE KRAGVHDGHL -99
HSV1-Patton   APVGTQQKPT GPTQRHTYYS ECDEFRFIAP RVLDEDAPPE KRAGVHDGHL -99
HSV1-DJl      APVGTQQKPT GPTQRHTYYS ECDEFRFIAP RVLDEDAPPE KRAGVHDGHL -99
HSV1-F        APVGTQQKPT GPTQRHTYYS ECDEFRFIAP RVLDEDAPPE KRAGVHDGHL -99

HSV2-MS       RRAPKVYCGG DERDVLRVGP EGFWPRRLRL WGGADHAPKG FDPTVTVFHV -150
HSV2-186      RRAPKVYCGG DERDVLRVGP EGFWPRRLRL WGGADHAPEG FDPTVTVFHV -150
HSV-Kos       KRAPKVYCGG DERDVLRVGS GGFWPRRSRL WGGVDHAPAG FNPTVTVFHV -149
HSV1-Patton   KRAPKVYCGG DERDVLRVGS GGFWPRRSRL WGGVDHAPAG FNPTVTVFHV -149
HSV1-DJL      KRAPKVYCGG DERDVLRVGS GGFWPRRSRL WGGVDHAPAG FNPTVTVFHV -149
HSV1-F        KRAPKVYCGG DERDVLRVGS GGFWPRRSRL WGGVDHAPAG FNPTVTVFHV -149

HSV2-MS       YDILEHVEHA YSMRAAQLHE RFMDAITPAG TVITLLGLTP EGHRVAVHVY -200
HSV2-186      YDILEHVEHA YSMRAAQLHE RFMDAITPAG TVITLLGLTP EGHRVAVHVY -200
HSV-Kos       YDILENVEHA YGMRAAQFHA RFMDAITPTG TVITLLGLTP EGHRVAVHVY -199
HSV1-Patton   YDILENVEHA YGMRAAQFHA RFMDAITPTG TVITLLGLTP EGHRVAVHVY -199
HSV1-DJL      YDILENVEHA YGMRAAQFHA RFMDAITPTG TVITLLGLTP EGHRVAVHVY -199
HSV1-F        YDILENVEHA YGMRAAQFHA RFMDAITPTG TVITLLGLTP EGHRVAVHVY -199

HSV2-MS       GTRQYFYMNK AEVDRHLQCR APRDLCERLA AALRESPGAS FRGISADHFE -250
HSV2-186      GTRQYFYMNK AEVDRHLQCR APRDLCERLA AALRESPGAS FRGISADHFE -250
HSV-Kos       GTRQYFYMNK EEVDRHLQCR APRDLCERMA AALRESPGAS FRGISADHFE -249
HSV1-Patton   GTRQYFYMNK EEVDRHLQCR APRDLCERMA AALRESPGAS FRGISADHFE -249
HSV1-DJL      GTRQYFYMNK EEVDRHLQCR APRDLCERMA AALRESPGAS FRGISADHFE -249
HSV1-F        GTRQYFYMNK EEVDRHLQCR APRDLCERMA AALRESPGAS FRGISADHFE -249

HSV2-MS       AEVVERADVY YYETRPTLYY RVFVRSGRAL AYLCDNFCPA IRKYEGGVDA -300
HSV2-186      AEVVERADVY YYETRPTLYY RVFVRSGRAL AYLCDNFCPA IRKYEGGVDA -300
HSV-Kos     AEVVERTDVY YYETRPALFY RVYVRSGRVL SYLCDNFCPA IKKYEGGVDA   -299
HSV1-Patton   AEVVERTDVY YYETRPALFY RVYVRSGRVL SYLCDNFCPA IKKYEGGVDA -299
HSV1-DJL      AEVVERTDVY YYETRPALFY RVYVRSGRVL SYLCDNFCPA IKKYEGGVDA -299
HSV1-F        AEVVERTDVY YYETRPALFY RVYVRSGRVL SYLCDNFCPA IKKYEGGVDA -299

HSV2-MS       TTRFILDNPG FVTFGWYRLK PGRGNAPAQP RPPTAFGTSS DVEFNCTADN -350
HSV2-186      TTRFILDNPG FVTFGWYRLK PGRGNAPAQP RPPTAFGTSS DVEFNCTADN -350
HSV-Kos       TTRFILDNPG FVTFGWYRLK PGRNNTLAQP RAPMAFGTSS DVEFNCTADN -349
HSV1-Patton   TTRFILDNPG FVTFGWYRLK PGRNNTLAQP RAPMAFGTSS DVEFNCTADN -349
HSV1-DJL      TTRFILDNPG FVTFGWYRLK PGRNNTLAQP RAPMAFGTSS DVEFNCTADN -349
HSV1-F        TTRFILDNPG FVTFGWYRLK PGRNNTLAQP RAPMAFGTSS DVEFNCTADN -349

HSV2-MS       LAVEGAMCDL PAYKLMCFDI ECKAGGEDEL AFPVAERPED LVIQISCLLY -400
HSV2-186      LAVEGAMCDL PAYKLMCFDI ECKAGGEDEL AFPVAERPED LVIQISCLLY -400
HSV-Kos       LAIEGGMSDL PAYKLMCFDI ECKAGGEDEL AFPVAGHPED LVIQISCLLY -399
HSV1-Patton   LAIEGGMSDL PAYKLMCFDI ECKAGGEDEL AFPVAGHPED LVIQISCLLY -399
HSV1-DJL      LAIEGGMSDL PAYKLMCFDI ECKAGGEDEL AFPVAGHPED LVIQISCLLY -399
HSV1-F        LAIEGGMSDL PAYKLMCFDI ECKAGGEDEL AFPVAGHPED LVIQISCLLY -399

HSV2-MS       DLSTTALEHI LLFSLGSCDL PESHLSDLAS RGLPAPVVLE FDSEFEMLLA -450
HSV2-186      DLSTTALEHI LLFSLGSCDL PESHLSDLAS RGLPAPVVLE FDSEFEMLLA -450
HSV-Kos       DLSTTALEHV LLFSLGSCDL PESHLNELAA RGLPTPVVLE FDSEFEMLLA -449
HSV1-Patton   DLSTTALEHV LLFSLGSCDL PESHLNELAA RGLPTPVVLE FDSEFEMLLA -449
HSV1-DJL      DLSTTALEHV LLFSLGSCDL PESHLNELAA RGLPTPVVLE FDSEFEMLLA -449
HSV1-F        DLSTTALEHV LLFSLGSCDL PESHLNELAA RGLPTPVVLE FDSEFEMLLA -449
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HSV2-MS       FMTFVKQYGP EFVTGYNIIN FDWPFVLTKL TEIYKVPLDG YGRMNGRGVF -500
HSV2-186      FMTFVKQYGP EFVTGYNIIN FDWPFVLTKL TEIYKVPLDG YGRMNGRGVF -500
HSV-Kos       FMTLVKQYGP EFVTGYNIIN FDWPFLLAKL TDIYKVPLDG YGRMNGRGVF -499
HSV1-Patton   FMTLVKQYGP EFVTGYNIIN FDWPFLLAKL TDIYKVPLDG YGRMNGRGVF -499
HSV1-DJL      FMTLVKQYGP EFVTGYNIIN FDWPFLLAKL TDIYKVPLDG YGRMNGRGVF -499
HSV1-F        FMTLVKQYGP EFVTGYNIIN FDWPFLLAKL TDIYKVPLDG YGRMNGRGVF -499

HSV2-MS       RVWDIGQSHF QKRSKIKVNG MVNIDMYGII TDKVKLSSYK LNAVAEAVLK -550
HSV2-186      RVWDIGQSHF QKRSKIKVNG MVNIDMYGII TDKVKLSSYK LNAVAEAVLK -550
HSV-Kos       RVWDIGQSHF QKRSKIKVNG MVNIDMYGII TDKIKLSSYK LNAVAEAVLK -549
HSV1-Patton   RVWDIGQSHF QKRSKIKVNG MVNIDMYGII TDKIKLSSYK LNAVAEAVLK -549
HSV1-DJL      RVWDIGQSHF QKRSKIKVNG MVNIDMYGII TDKIKLSSYK LNAVAEAVLK -549
HSV1-F        RVWDIGQSHF QKRSKIKVNG MVNIDMYGII TDKIKLSSYK LNAVAEAVLK -549

HSV2-MS       DKKKDLSYRD IPAYYASGPA QRGVIGEYCV QDSLLVGQLF FKFLPHLELS -600
HSV2-186      DKKKDLSYRD IPAYYASGPA QRGVIGEYCV QDSLLVGQLF FKFLPHLELS -600
HSV-Kos       DKKKDLSYRD IPAYYAAGPA QRGVIGEYCI QDSLLVGQLF FKFLPHLELS -599
HSV1-Patton   DKKKDLSYRD IPAYYAAGPA QRGVIGEYCI QDSLLVGQLF FKFLPHLELS -599
HSV1-DJL      DKKKDLSYRD IPTYYAAGPA QRGVIGEYCI QDSLLVGQLF FKFLPHLELS -599
HSV1-F        DKKKDLSYRD IPAYYAAGPA QRGVIGEYCI QDSLLVGQLF FKFLPHLELS -599

HSV2-MS       AVARLAGINI TRTIYDGQQI RVFTCLLRLA GQKGFILPDT QGRFRGLDKE -650
HSV2-186      AVARLAGINI TRTIYDGQQI RVFTCLLRLA GQKGFILPDT QGRFRGLDKE -650
HSV-Kos       AVARLAGINI TRTIYDGQQI RVFTCLLRLA DQKGFILPDT QGRFRGAGGE -649
HSV1-Patton   AVARLAGINI TRTIYDGQQI RVFTCLLRLA DQKGFILPDT QGRFRGAGGE -649
HSV1-DJL      AVARLAGINI TRTIYDGQQI RVFTCLLRLA DQKGFILPDT QGRFRGAGGE -649
HSV1-F        AVARLAGINI TRTIYDGQQI RVFTCLLRLA DQKGFILPDT QGRFRGGGGE -649

HSV2-MS       APKRPAVPRG EGERPGDGNG DEDKDDDE.. DEDGDERE.E VARETGGRHV -697
HSV2-186      APKRPAVPRG EGERPGDGNG DEDKDDDEDG DEDGDERE.E VARETGGRHV -697
HSV-Kos       APKRPAAARE DEERP..... EEEGEDEDER EEGGGEREPE GARETAGRHV -694
HSV1-Patton   APKRPAAARE DEERP..... EEEGEDEDER EEGGGEREPE GARETAGRHV -694
HSV1-DJL      APKRPAAARE DEERP..... EEEGEDENER EEGGGEREPE GARETAGRHV -694
HSV1-F        APKRPAAARE DEERP..... EEEGEDEDER EEGGGEREPE GARETAGRHV -694

HSV2-MS       GYQGARVLDP TSGFHVDPVV VFDFASLYPS IIQAHNLCFS TLSLRPEAVA -747
HSV2-186      GYQGARVLDP TSGFHVDPVV VFDFASLYPS IIQAHNLCFS TLSLRPEAVA -749
HSV-Kos       GYQGARVLDP TSGFHVNPVV VFDFASLYPS IIQAHNLCFS TLSLRADAVA -744
HSV1-Patton   GYQGARVLDP ISGFHVNPVV VFDFASLYPS IIQAHNLCFS TLSLRADAVA -744
HSV1-DJL      GYQGARVLDP TSGFHVNPVV VFDFASLYPS IIQAHNLCFS TLSLRADAVA -744
HSV1-F        GYQGARVLDP TSGFHVNPVV VFDFASLYPS IIQAHNLCFS TLSLRADAVA -744

HSV2-MS       HLEADRDYLE IEVGGRRLFF VKAHVRESLL SILLRDWLAM RKQIRSRIPQ -797
HSV2-186      HLEADRDYLE IEVGGRRLFF VKAHVRESLL SILLRDWLAM RKQIRSRIPQ -799
HSV-Kos       HLEAGKDYLE IEVGGRRLFF VKAHVRESLL SILLRDWLAM RKQIRSRIPQ -794
HSV1-Patton   HLEAGKDYLE IEVGGRRLFF VKAHVRESLL SILLRDWLAM RKQIRSRIPQ -794
HSV1-DJL      HLEAGKDYLE IEVGGRRLFF VKAHVRESLL SILLRDWLAM RKQIRSRIPQ -794
HSV1-F        HLEAGKDYLE IEVGGRRLFF VKAHVRESLL SILLRDWLAM RKQIRSRIPQ -794

HSV2-MS       STPEEAVLLD KQQAAIKVVC NSVYGFTGVQ HGLLPCLHVA ATVTTIGREM -847
HSV2-186      SPPEEAVLLD KQQAAIKVVC NSVYGFTGVQ HGLLPCLHVA ATVTTIGREM -849
HSV-Kos       SSPEEAVLLD KQQAAIKVVC NSVYGFTGVQ HGLLPCLHVA ATVTTIGREM -844
HSV1-Patton   SSPEEAVLLD KQQAAIKVVC NSVYGFTGVQ HGLLPCLHVA ATVTTIGREM -844
HSV1-DJL      SSPEEAVLLD KQQAAIKVVC NSVYGFTGVQ HGLLPCLHVA ATVTTIGREM -844
HSV1-F        SSPEEAVLLD KQQAAIKVVC NSVYGFTGVQ HGLLPCLHVA ATVTTIGREM -844

HSV2-MS       LLATRAYVHA RWAEFDQLLA DFPEAAGMRA PGPYSMRIIY GDTDSIFVLC -897
HSV2-186      LLATRAYVHA RWAEFDQLLA DFPEAAGMRA PGPYSMRIIY GDTDSIFVLC -899
HSV-Kos       LLATREYVHA RWAAFEQLLA DFPEAADMRA PGPYSMRIIY GDTDSIFVLC -894
HSV1-Patton   LLATREYVHA RWAAFEQLLA DFPEAADMRA PGPYSMRIIY GDTDSIFVLC -894
HSV1-DJL      LLATREYVHA RWAAFEQLLA DFPEAADMRA PGPYSMRIIY GDTDSIFVLC -894
HSV1-F        LLATREYVHA RWAAFEQLLA DFPEAADMRA PGPYSMRIIY GDTDSIFVLC -894

HSV2-MS       RGLTAAGLVA MGDKMASHIS RALFLPPIKL ECEKTFTKLL LIAKKKYIGV -947
HSV2-186      RGLTAAGLVA MGDKMASHIS RALFLPPIKL ECEKTFTKLL LIAKKKYIGV -949
HSV-Kos       RGLTAAGLTA MGDKMASHIS RALFLPPIKL ECEKTFTKLL LIAKKKYIGV -944
HSV1-Patton   RGLTAAGLTA MGDKMASHIS RALFLPPIKL ECEKTFTKLL LIAKKKYIGV -944
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HSV1-DJL      RGLTAAGLTA VGDKMASHIS RALFLPPIKL ECEKTFTKLL LIAKKKYIGV -944
HSV1-F        RGLTAAGLTA VGDKMASHIS RALFLSPIKL ECEKTFTKLL LIAKKKYIGV -944

HSV2-MS       ICGGKMLIKG VDLVRKNNCA FINRTSRALV DLLFYDDTVS GAAAALAERP -997
HSV2-186      ICGGKMLIKG VDLVRKNNCA FINRTSRALV DLLFYDDTVS GAAAALAERP -999
HSV-Kos       IYGGKMLIKG VDLVRKNNCA FINRTSRALV DLLFYDDTVS GAAAALAERP -994
HSV1-Patton   IYGGKMLIKG VDLVRKNNCA FINRTSRALV DLLFYDDTVS GAAAALAERP -994
HSV1-DJL      IYGGKMLIKG VDLVRKNNCA FINRTSRALV DLLFYDDTVS GAAAALAERP -994
HSV1-F        IYGGKMLIKG VDLVRKNNCA FINRTSRALV DLLFYDDTVS GAAAALAERP -994

HSV2-MS       AEEWLARPLP EGLQAFGAVL VDAHRRITDP ERDIQDFVLT AELSRHPRAY -1047
HSV2-186      AEEWLARPLP EGLQAFGAVL VDAHRRITDP ERDIQDFVLT AELSRHPRAY -1049
HSV-Kos       AEEWLARPLP EGLQAFGAVL VDAHRRITDP ERDIQDFVLT AELSRHPRAY -1044
HSV1-Patton   AEEWLARPLP EGLQAFGAVL VDAHRRITDP ERDIQDFVLT AELSRHPRAY -1044
HSV1-DJL      AEEWLARPLP EGLQAFGAVL VDAHRRITDP ERDIQDFVLT AELSRHPRAY -1044
HSV1-F        AEEWLARPLP EGLQAFGAVL VDAHRRITDP ERDIQDFVLT AELSRHPRAY -1044

HSV2-MS       TNKRLAHLTV YYKLMARRAQ VPSIKDRIPY VIVAQTREVE ETVARLAALR -1097
HSV2-186      TNKRLAHLTV YYKLMARRAQ VPSIKDRIPY VIVAQTREVE ETVARLAALR -1099
HSV-Kos       TNKRLAHLTV YYKLMARRAQ VPSIKDRIPY VIVAQTREVE ETVARLAALR -1094
HSV1-Patton   TNKRLAHLTV YYKLMARRAQ VPSIKDRIPY VIVAQTREVE ETVARLAALR -1094
HSV1-DJL      TNKRLAHLTV YYKLMARRAQ VPSIKDRIPY VIVAQTREVE ETVARLAALR -1094
HSV1-F        TNKRLAHLTV YYKLMARRAQ VPSIKDRIPY VIVAQTREVE ETVARLAALR -1094

HSV2-MS       ELDAAAPGDE PAPPAALPSP AKRPRETPSH ADPPGGASKP RKLLVSELAE -1147
HSV2-186      ELDAAAPGDE PAPPAALPSP AKRPRETPSH ADPPGGASKP RKLLVSELAE -1149
HSV-Kos       ELDAAAPGDE PAPPAALPSP AKRPRETPSH ADPPGGASKP RKLLVSELAE -1144
HSV1-Patton   ELDAAAPGDE PAPPAALPSP AKRPRETPSP ADPPGGASKP RKLLVSELAE -1144
HSV1-DJL      ELDAAAPGDE PAPPAALPSP AKRPRETPSP ADPPGGASKP RKLLVSELAE -1144
HSV1-F        ELDAAAPGDE PAPPAALPSP AKRPRETPLH ADPPGGASKP RKLLVSELAE -1144

HSV2-MS       DPGYAIARGV PLNTDYYFSH LLGAACVTFK ALFGNNAKIT ESLLKRFIPE -1197
HSV2-186      DPGYAIARGV PLNTDYYFSH LLGAACVTFK ALFGNNAKIT ESLLKRFIPE -1199
HSV-Kos       DPAYAIAHGV ALNTDYYFSH LLGAACVTFK ALFGNNAKIT ESLLKRFIPE -1194
HSV1-Patton   DPAYAIAHGV ALNTDYYFSH LLGAACVTFK ALFGNNAKIT ESLLKRFIPE -1194
HSV1-DJL      DPAYAIAHGV ALNTDYYFSH LLGAACVTFK ALFGNNAKIT ESLLKRFIPE -1194
HSV1-F        DPAYAIAHGV ALNTDYYFSH LLGAACVTFK ALFGNNAKIT ESLLKRFIPE -1194

HSV2-MS       TWHPPDDVAA RLRAAGFGPA GAGATAEETR RMLHRAFDTL A* -1238
HSV2-186      TWHPPDDVAA RLRAAGFGPA GAGATAEETR RMLHRAFDTL A* -1240
HSV-Kos       VWHPPDDVAA RLRAAGFGAV GAGATAEETR RMLHRAFDTL A* -1235
HSV1-Patton   VWHPPDDVTA RLRAAGFGAV GAGATAEETR RMLHRAFDTL A* -1235
HSV1-DJL      VWHPPDDVAA RLRTAGFGAV GAGATAEETR RMLHRAFDTL A* -1235
HSV1-F        VWHPPDDVAA RLRAAGFGAV GAGATAEETR RMLHRAFDTL A* -1235
```

*Amino acid alignment demonstrates difference in amino acid's sequences.

*The gaps "....." indicate missing amino acids relative to other stanins.

*Wild HSV2-MS is listed as SEQ. ID NO 14.

*Wild HSV2-186 is listed as SEQ. ID NO 15.

*Wild HSV-Kos is listed as SEQ. ID NO 16.

*Wild HSV1-Patton is listed as SEQ. ID NO 17.

*Wild HSV1-DJL is listed as SEQ. ID NO 18.

*Wild HSV1-F is listed as SEQ. ID NO 19.

Figure 5 DNA and amino acid sequence list

SEQ. ID. NO. 1 DNA sequence of DNA polymerase gene for HSV2-MS-M1

1 ATGTTTTGTG CCGCGGGCGG CCCGACTTCC CCCGGGGGGA AGTCGGCGGC

51 TCGGGCGGCG TCTGGGTTTT TTGCCCCCCA CAACCCCCGG GGAGCCACCC

101 AGACGGCACC GCCGCCTTGC CGCCGGCAGA ACTTCTACAA CCCCCACCTC

151 GCTCAGACCG GAACGCAGCC AAAGGCCCCC GGGCCGGCTC AGCGCCATAC

201 GTACTACAGC GAGTGCGACG AATTTCGATT TATCGCCCCG CGTTCGCTGG

251 ACGAGGACGC CCCCGCGGAG CAGCGCACCG GGGTCCACGA CGGCCGCCTC

301 CGGCGCGCCC CTAAGGTGTA CTGCGGGGGG GACGAGCGCG ACGTCCTCCG

351 CGTGGGCCCG GAGGGCTTCT GGCCGCGTCG CTTGCGCCTG TGGGGCGGTG

401 CGGACCATGC CCCCAAGGGG TTCGACCCCA CCGTCACCGT CTTCCACGTG

451 TACGACATCC TGGAGCACGT GGAACACGCG TACAGCATGC GCGCCGCCCA

501 GCTCCACGAG CGATTTATGG ACGCCATCAC GCCCGCCGGG ACCGTCATCA

551 CGCTTCTGGG TCTGACCCCC GAAGGCCATC GCGTCGCCGT TCACGTCTAC

601 GGCACGCGGC AGTACTTTTA CATGAACAAG GCGGAGGTGG ATCGGCACCT

651 GCAGTGCCGT GCCCCGCGCG ATCTCTGCGA GCGCCTGGCG GCGGCCCTGC

701 GCGAGTCGCC GGGGGCGTCG TTCCGCGGCA TCTCCGCGGA CCACTTCGAG

751 GCGGAGGTGG TGGAGCGCGC CGACGTGTAC TATTACGAAA CGCGCCCGAC

801 CCTGTACTAC CGCGTCTTCG TGCGAAGCGG GCGCGCGCTG GCCTACCTGT

851 GCGACAACTT TTGCCCCGCG ATCAGGAAGT ACGAGGGGGG CGTCGACGCC

901 ACCACCCGGT TTATCCTGGA CAACCCGGGG TTTGTCACCT TCGGCTGGTA

951 CCGCCTCAAG CCCGGCCGCG GGAACGCGCC GGCCCAACCG CGCCCCCCGA

1001 CGGCGTTCGG AACCTCGAGC GACGTCGAGT TTAACTGCAC GGCGGACAAC

1051 CTGGCCGTCG AGGGGGCCAT GTGTGACCTG CCGGCCTACA AGCTCATGTG

1101 CTTCGATATC GAATGCAAGG CCGGGGGGGA GGACGAGCTG GCCTTTCCGG

1151 TCGCGGAACG CCCGGAAGAC CTCGTCATCC AGATCTCCTG TCTGCTCTAC

1201 GACCTGTCCA CCACCGCCCT CGAGCACATC CTCCTGTTTT CGCTCGGATC

1251 CTGCGACCTC CCCGAGTCCC ACCTCAGCGA TCTCGCCTCC AGGGGCCTGC

1301 CGGCCCCCGT CGTCCTGGAG TTTGACAGCG AATTCGAGAT GCTGCTGGCC

1351 TTCATGACCT TCGTCAAGCA GTACGGCCCC GAGTTCGTGA CCGGGTACAA

1401 CATCATCAAC TTCGACTGGC CCTTCGTCCT GACCAAGCTG ACGGAGATCT

1451 ACAAGGTCCC GCTCGACGGG TACGGGCGCA TGAACGGCCG GGGTGTGTTC

1501 CGCGTGTGGG ACATCGGCCA GAGCCACTTT CAGAAGCGCA GCAAGATCAA

1551 GGTGAACGGG ATGGTGAACA TCGACATGTA CGGCATCATC ACCGACAAGG

1601 TCAAACTCTC CAGCTACAAG CTGAACGCCG TCGCCGAGGC CGTCTTGAAG

1651 GACAAGAAGA AGGATCTGAG CTACCGCGAC ATCCCCGCCT ACTACGCCTC

1701 CGGGCCCGCG CAGCGCGGGG TGATCGGCGA GTATTGTGTG CAGGACTCGC

1751 TGCTGGTCGG GCAGCTGTTC TTCAAGTTTC TGCCGCACCT GGAGCTTTCC

1801 GCCGTCGCGC GCCTGGCGGG CATCAACATC ACCCGCACCA TCTACGACGG

1851 CCAGCAGATC CGCGTCTTCA CGTGCCTCCT GCGCCTTGCG GGCCAGAAGG

1901 GCTTCATCCT GCCGGACACC CAGGGGCGGT TTCGGGGCCT CGACAAGGAG

1951 GCGCCCAAGC GCCCGGCCGT GCCTCGGGGG GAAGGGGAGC GGCCGGGGGA

2001 CGGGAACGGG GACGAGGATA AGGACGACGA CGAGGACGAG GACGGGGACG

2051 AGCGCGAGGA GGTCGCGCGC GAGACCGGGG GCCGGCACGT TGGGTACCAG

2101 GGGGCCCGGG TCCTCGACCC CACCTCCGGG TTTCACGTCG ACCCCGTGGT

2151 GGTGTTTGAC TTTGCCAGCC TGTACCCCAG CATCATCCAG GCCCACAACC

2201 TGTGCTTCAG TACGCTCTCC CTGCGGCCCG AGGCCGTCGC GCACCTGGAG

2251 GCGGACCGGG ACTACCTGGA GATCGAGGTG GGGGGCCGAC GGCTGTTCTT

2301 CGTGAAGGCC CACGTACGCG AGAGCCTGCT GAGCATCCTG CTGCGCGACT

2351 GGCTGGCCAT GCGAAAGCAG ATCCGCTCGC GGATCCCCCA GAGCACCCCC

2401 GAGGAGGCCG TCCTCCTCGA CAAGCAACAG GCCGCCATCA AGGTGGTGTG

2451 CAACTCGGTG TACGGGTTCA CCGGGGCGCA GCACGGTCTT CTGCCCTGCC

2501 TGCACGTGGC CGCCACCGTG ACGACCATCG GCCGCGAGAT GCTCCTCGCG

2551 ACGCGCGCGT ACGTGCACGC GCGCTGGGCG GAGTTCGATC AGCTGCTGGC

2601 CGACTTTCCG GAGGCGGCCG GCATGCGCGC CCCCGGTCCG TACTCCATGC

2651 GCATCATCTA CGGGGACACG GACTCCATTT TCGTTTTGTG CCGCGGCCTC

2701 ACGGCCGCGG GCCTGGTGGC CATGGGCGAC AAGATGGCGA GCCACATCTC

2751 GCGCGCGCTG TTCCTCCCCC CGATCAAGCT CGAGTGCGAA AAAACGTTCA

2801 CCAAGCTGCT GCTCATCGCC AAGAAAAAGT ACATCGGCGT CATCTGCGGG

2851 GGCAAGATGC TCATCAAGGG CGTGGATCTG GTGCGCAAAA ACAACTGCGC

2901 GTTTATCAAC CGCACCTCCA GGGCCCTGGT CGACCTGCTG TTTTACGACG

2951 ATACCGTATC CGGAGCGGCC GCCGCGTTAG CCGAGCGCCC CGCAGAGGAG

3001 TGGCTGGCGC GACCCCTGCC CGAGGGACTG CAGGCGTTCG GGGCCGTCCT

3051 CGTAGACGCC CATCGGCGCA TCACCGACCC GGAGAGGGAC ATCCAGGACT

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3151 CGCCTGGCCC ACCTGACGGT GTATTACAAG CTCATGGCCC GCCGCGCGCA

3201 GGTCCCGTCC ATCAAGGACC GGATCCCGTA CGTGATCGTG GCCCAGACCC

3251 GCGAGGTAGA GGAGACGGTC GCGCGGCTGG CCGCCCTCCG CGAGCTAGAC

3301 GCCGCCGCCC CAGGGGACGA GCCCGCCCCC CCAGCGGCCC TGCCCTCCCC

3351 GGCCAAGCGC CCCCGGGAGA CGCCGTCGCA TGCCGACCCC CCGGGAGGCG

3401 CGTCCAAGCC CCGCAAGCTG CTGGTGTCCG AGCTGGCGGA GGATCCCGGG

3451 TACGCCATCG CCCGGGGCGT TCCGCTCAAC ACGGACTATT ACTTCTCGCA

3501 CCTGCTGGGG GCGGCCTGCG TGACGTTCAA GGCCCTGTTT GGAAATAACG

3551 CCAAGATCAC CGAGAGTCTG TTAAAGAGGT TTATTCCCGA GACGTGGCAC

3601 CCCCCGGACG ACGTGGCCGC GCGGCTCAGG GCCGCGGGGT TCGGGCCGGC

3651 GGGGGCCGGC GCTACGGCGG AGGAAACTCG TCGAATGTTG CATAGAGCCT

3701 TTGATACTCT AGCATGA

SEQ. ID. NO. 2 Amino acid sequence of DNA polymerase for HSV2-MS-M1

1 MFCAAGGPTS PGGKSAARAA SGFFAPHNPR GATQTAPPPC RRQNFYNPHL

51 AQTGTQPKAP GPAQRHTYYS ECDEFRFIAP RSLDEDAPAE QRTGVHDGRL

101 RRAPKVYCGG DERDVLRVGP EGFWPRRLRL WGGADHAPKG FDPTVTVFHV

151 YDILEHVEHA YSMRAAQLHE RFMDAITPAG TVITLLGLTP EGHRVAVHVY

201 GTRQYFYMNK AEVDRHLQCR APRDLCERLA AALRESPGAS FRGISADHFE

251 AEVVERADVY YYETRPTLYY RVFVRSGRAL AYLCDNFCPA IRKYEGGVDA

301 TTRFILDNPG FVTFGWYRLK PGRGNAPAQP RPPTAFGTSS DVEFNCTADN

351 LAVEGAMCDL PAYKLMCFDI ECKAGGEDEL AFPVAERPED LVIQISCLLY

401 DLSTTALEHI LLFSLGSCDL PESHLSDLAS RGLPAPVVLE FDSEFEMLLA

451 FMTFVKQYGP EFVTGYNIIN FDWPFVLTKL TEIYKVPLDG YGRMNGRGVF

501 RVWDIGQSHF QKRSKIKVNG MVNIDMYGII TDKVKLSSYK LNAVAEAVLK

551 DKKKDLSYRD IPAYYASGPA QRGVIGEYCV QDSLLVGQLF FKFLPHLELS

601 AVARLAGINI TRTIYDGQQI RVFTCLLRLA GQKGFILPDT QGRFRGLDKE

651 APKRPAVPRG EGERPGDGNG DEDKDDDEDE DGDEREEVAR ETGGRHVGYQ

701 GARVLDPTSG FHVDPVVVFD FASLYPSIIQ AHNLCFSTLS LRPEAVAHLE

751 ADRDYLEIEV GGRRLFFVKA HVRESLLSIL LRDWLAMRKQ IRSRIPQSTP

801 EEAVLLDKQQ AAIKVVCNSV YGFTGAQHGL LPCLHVAATV TTIGREMLLA

851 TRAYVHARWA EFDQLLADFP EAAGMRAPGP YSMRIIYGDT DSIFVLCRGL

901 TAAGLVAMGD KMASHISRAL FLPPIKLECE KTFTKLLLIA KKKYIGVICG

951 GKMLIKGVDL VRKNNCAFIN RTSRALVDLL FYDDTVSGAA AALAERPAEE

1001 WLARPLPEGL QAFGAVLVDA HRRITDPERD IQDFVLTAEL SRHPRAYTNK

1051 RLAHLTVYYK LMARRAQVPS IKDRIPYVIV AQTREVEETV ARLAALRELD

1101 AAAPGDEPAP PAALPSPAKR PRETPSHADP PGGASKPRKL LVSELAEDPG

1151 YAIARGVPLN TDYYFSHLLG AACVTFKALF GNNAKITESL LKRFIPETWH

1201 PPDDVAARLR AAGFGPAGAG ATAEETRRML HRAFDTLA*

SEQ.ID.NO. 3 DNA sequence of DNA polymerase gene for HSV2-186-M1

1 ATGTTTTGTG CCGCGGGCGG CCCGGCTTCC CCCGGGGGGA AGTCGGCGGC

51 TCGGGCGGCG TCTGGGTTTT TTGCCCCCCA CAACCCCCGG GGAGCCACCC

101 AGACGGCACC GCCGCCTTGC CGCCGGCAGA ACTTCTACAA CCCCCACCTC

151 GCTCAGACCG GAACGCAGCC AAAGGCCCCC GGGCCGGCTC AGCGCCATAC

201 GTACTACAGC GAGTGCGACG AATTTCGATT TATCGCCCCG CGTTCGCTGG

251 ACGAGGACGC CCCCGCGGAG CAGCGCACCG GGGTCCACGA CGGCCGCCTC

301 CGGCGCGCCC CTAAGGTGTA CTGCGGGGGG GACGAGCGCG ACGTCCTCCG

351 CGTGGGCCCG GAGGGCTTCT GGCCGCGTCG CTTGCGCCTG TGGGGCGGTG

401 CGGACCATGC CCCCGAGGGG TTCGACCCCA CCGTCACCGT CTTCCACGTG

451 TACGACATCC TGGAGCACGT GGAACACGCG TACAGCATGC GCGCCGCCCA

501 GCTCCACGAG CGATTTATGG ACGCCATCAC GCCCGCCGGG ACCGTCATCA

551 CGCTTCTGGG TCTGACCCCC GAAGGCCATC GCGTCGCCGT TCACGTCTAC

601 GGCACGCGGC AGTACTTTTA CATGAACAAG GCGGAGGTGG ATCGGCACCT

651 GCAGTGCCGT GCCCCGCGCG ATCTCTGCGA GCGCCTGGCG GCGGCCCTGC

701 GCGAGTCGCC GGGGGCGTCG TTCCGCGGCA TCTCCGCGGA CCACTTCGAG

751 GCGGAGGTGG TGGAGCGCGC CGACGTGTAC TATTACGAAA CGCGCCCGAC

801 CCTGTACTAC CGCGTCTTCG TGCGAAGCGG GCGCGCGCTG GCCTACCTGT

851 GCGACAACTT TTGCCCCGCG ATCAGGAAGT ACGAGGGGGG CGTCGACGCC

901 ACCACCCGGT TTATCCTGGA CAACCCGGGG TTTGTCACCT TCGGCTGGTA

951 CCGCCTCAAG CCCGGCCGCG GGAACGCGCC GGCCCAACCG CGCCCCCCGA

1001 CGGCGTTCGG AACCTCGAGC GACGTCGAGT TTAACTGCAC GGCGGACAAC

1051 CTGGCCGTCG AGGGGGCCAT GTGTGACCTG CCGGCCTACA AGCTCATGTG

1101 CTTCGATATC GAATGCAAGG CCGGGGGGGA GGACGAGCTG GCCTTTCCGG

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1201 GACCTGTCCA CCACCGCCCT CGAGCACATC CTCCTGTTTT CGCTCGGATC

1251 CTGCGACCTC CCCGAGTCCC ACCTCAGCGA TCTCGCCTCC AGGGGCCTGC

1301 CGGCCCCCGT CGTCCTGGAG TTTGACAGCG AATTCGAGAT GCTGCTGGCC

1351 TTCATGACCT TCGTCAAGCA GTACGGCCCC GAGTTCGTGA CCGGGTACAA

1401 CATCATCAAC TTCGACTGGC CCTTCGTCCT GACCAAGCTG ACGGAGATCT

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2001 CGGGAACGGG GACGAGGATA AGGACGACGA CGAGGACGGG GACGAGGACG

2051 GGGACGAGCG CGAGGAGGTC GCGCGCGAGA CCGGGGGCCG GCACGTTGGG

2101 TACCAGGGGG CCCGGGTCCT CGACCCCACC TCCGGGTTTC ACGTCGACCC

2151 CGTGGTGGTG TTTGACTTTG CCAGCCTGTA CCCCAGCATC ATCCAGGCCC

2201 ACAACCTGTG CTTCAGTACG CTCTCCCTGC GGCCCGAGGC CGTCGCGCAC

2251 CTGGAGGCGG ACCGGGACTA CCTGGAGATC GAGGTGGGGG GCCGACGGCT

2301 GTTCTTCGTG AAGGCCCACG TACGCGAGAG CCTGCTGAGC ATCCTGCTGC

2351 GCGACTGGCT GGCCATGCGA AAGCAGATCC GCTCGCGGAT CCCCCAGAGC

2401 CCCCCCGAGG AGGCCGTCCT CCTCGACAAG CAACAGGCCG CCATCAAGGT

2451 GGTGTGCAAC TCGGTGTACG GGTTCACCGG GGCGCAGCAC GGTCTTCTGC

2501 CCTGCCTGCA CGTGGCCGCC ACCGTGACGA CCATCGGCCG CGAGATGCTC

2551 CTCGCGACGC GCGCGTACGT GCACGCGCGC TGGGCGGAGT TCGATCAGCT

2601 GCTGGCCGAC TTTCCGGAGG CGGCCGGCAT GCGCGCCCCC GGTCCGTACT

2651 CCATGCGCAT CATCTACGGG GACACGGACT CCATTTTCGT TTTGTGCCGC

2701 GGCCTCACGG CCGCGGGCCT GGTGGCCATG GGCGACAAGA TGGCGAGCCA

2751 CATCTCGCGC GCGCTGTTCC TCCCCCCGAT CAAGCTCGAG TGCGAAAAAA

2801 CGTTCACCAA GCTGCTGCTC ATCGCCAAGA AAAAGTACAT CGGCGTCATC

2851 TGCGGGGGCA AGATGCTCAT CAAGGGCGTG GATCTGGTGC GCAAAAACAA

2901 CTGCGCGTTT ATCAACCGCA CCTCCAGGGC CCTGGTCGAC CTGCTGTTTT

2951 ACGACGATAC CGTATCCGGA GCGGCCGCCG CGTTAGCCGA GCGCCCCGCA

3001 GAGGAGTGGC TGGCGCGACC CCTGCCCGAG GGACTGCAGG CGTTCGGGGC

3051 CGTCCTCGTA GACGCCCATC GGCGCATCAC CGACCCGGAG AGGGACATCC

3101 AGGACTTTGT CCTCACCGCC GAACTGAGCA GACACCCGCG CGCGTACACC

3151 AACAAGCGCC TGGCCCACCT GACGGTGTAT TACAAGCTCA TGGCCCGCCG

3201 CGCGCAGGTC CCGTCCATCA AGGACCGGAT CCCGTACGTG ATCGTGGCCC

3251 AGACCCGCGA GGTAGAGGAG ACGGTCGCGC GGCTGGCCGC CCTCCGCGAG

3301 CTAGACGCCG CCGCCCCAGG GGACGAGCCC GCCCCCCCAG CGGCCCTGCC

3351 CTCCCCGGCC AAGCGCCCCC GGGAGACGCC GTCGCATGCC GACCCCCCGG

3401 GAGGCGCGTC CAAGCCCCGC AAGCTGCTGG TGTCCGAGCT GGCGGAGGAT

3451 CCCGGGTACG CCATCGCCCG GGGCGTTCCG CTCAACACGG ACTATTACTT

3501 CTCGCACCTG CTGGGGGCGG CCTGCGTGAC GTTCAAGGCC CTGTTTGGAA

3551 ATAACGCCAA GATCACCGAG AGTCTGTTAA AGAGGTTTAT TCCCGAGACG

3601 TGGCACCCCC CGGACGACGT GGCCGCGCGG CTCAGGGCCG CGGGGTTCGG

3651 GCCGGCGGGG GCCGGCGCTA CGGCGGAGGA AACTCGTCGA ATGTTGCATA

3701 GAGCCTTTGA TACTCTAGCA TGA

SEQ.ID.NO. 4 Amino acid sequence of DNA polymerase for HSV2-186-M1

1 MFCAAGGPAS PGGKSAARAA SGFFAPHNPR GATQTAPPPC RRQNFYNPHL

51 AQTGTQPKAP GPAQRHTYYS ECDEFRFIAP RSLDEDAPAE QRTGVHDGRL

101 RRAPKVYCGG DERDVLRVGP EGFWPRRLRL WGGADHAPEG FDPTVTVFHV

151 YDILEHVEHA YSMRAAQLHE RFMDAITPAG TVITLLGLTP EGHRVAVHVY

201 GTRQYFYMNK AEVDRHLQCR APRDLCERLA AALRESPGAS FRGISADHFE

251 AEVVERADVY YYETRPTLYY RVFVRSGRAL AYLCDNFCPA IRKYEGGVDA

301 TTRFILDNPG FVTFGWYRLK PGRGNAPAQP RPPTAFGTSS DVEFNCTADN

351 LAVEGAMCDL PAYKLMCFDI ECKAGGEDEL AFPVAERPED LVIQISCLLY

401 DLSTTALEHI LLFSLGSCDL PESHLSDLAS RGLPAPVVLE FDSEFEMLLA

451 FMTFVKQYGP EFVTGYNIIN FDWPFVLTKL TEIYKVPLDG YGRMNGRGVF

501 RVWDIGQSHF QKRSKIKVNG MVNIDMYGII TDKVKLSSYK LNAVAEAVLK

551 DKKKDLSYRD IPAYYASGPA QRGVIGEYCV QDSLLVGQLF FKFLPHLELS

601 AVARLAGINI TRTIYDGQQI RVFTCLLRLA GQKGFILPDT QGRFRGLDKE

651 APKRPAVPRG EGERPGDGNG DEDKDDDEDG DEDGDEREEV ARETGGRHVG

701 YQGARVLDPT SGFHVDPVVV FDFASLYPSI IQAHNLCFST LSLRPEAVAH

751 LEADRDYLEI EVGGRRLFFV KAHVRESLLS ILLRDWLAMR KQIRSRIPQS

801 PPEEAVLLDK QQAAIKVVCN SVYGFTGAQH GLLPCLHVAA TVTTIGREML

851 LATRAYVHAR WAEFDQLLAD FPEAAGMRAP GPYSMRIIYG DTDSIFVLCR

901 GLTAAGLVAM GDKMASHISR ALFLPPIKLE CEKTFTKLLL IAKKKYIGVI

951 CGGKMLIKGV DLVRKNNCAF INRTSRALVD LLFYDDTVSG AAAALAERPA

1001 EEWLARPLPE GLQAFGAVLV DAHRRITDPE RDIQDFVLTA ELSRHPRAYT

1051 NKRLAHLTVY YKLMARRAQV PSIKDRIPYV IVAQTREVEE TVARLAALRE

1101 LDAAAPGDEP APPAALPSPA KRPRETPSHA DPPGGASKPR KLLVSELAED

1151 PGYAIARGVP LNTDYYFSHL LGAACVTFKA LFGNNAKITE SLLKRFIPET

1201 WHPPDDVAAR LRAAGFGPAG AGATAEETRR MLHRAFDTLA *

SEQ.ID.NO. 5 DNA sequence of DNA polymerase gene for HSV1-KOS-M1

1 ATGTTTTCCG GTGGCGGCGG CCCGCTGTCC CCCGGAGGAA AGTCGGCGGC

51 CAGGGCGGCG TCCGGGTTTT TTGCGCCCGC CGGCCCTCGC GGAGCCGGCC

101 GGGGACCCCC GCCTTGTTTG AGGCAAAACT TTTACAACCC CTACCTCGCC

151 CCAGTCGGGA CGCAACAGAA GCCGACCGGG CCAACCCAGC GCCATACGTA

201 CTATAGCGAA TGCGATGAAT TTCGATTCAT CGCCCCGCGG GTGCTGGACG

251 AGGATGCCCC CCCGGAGAAG CGCGCCGGGG TGCACGACGG TCACCTCAAG

301 CGCGCCCCCA AGGTGTACTG CGGGGGGGAC GAGCGCGACG TCCTCCGCGT

351 CGGGTCGGGC GGCTTCTGGC CGCGGCGCTC GCGCCTGTGG GGCGGCGTGG

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451 GACATCCTGG AGAACGTGGA GCACGCGTAC GGCATGCGCG CGGCCCAGTT

501 CCACGCGCGG TTTATGGACG CCATCACACC GACGGGGACC GTCATCACGC

551 TCCTGGGCCT GACTCCGGAA GGCCACCGGG TGGCCGTTCA CGTTTACGGC

601 ACGCGGCAGT ACTTTTACAT GAACAAGGAG GAGGTTGACA GGCACCTACA

651 ATGCCGCGCC CCACGAGATC TCTGCGAGCG CATGGCCGCG GCCCTGCGCG

701 AGTCCCCGGG CGCGTCGTTC CGCGGCATCT CCGCGGACCA CTTCGAGGCG

751 GAGGTGGTGG AGCGCACCGA CGTGTACTAC TACGAGACGC GCCCCGCTCT

801 GTTTTACCGC GTCTACGTCC GAAGCGGGCG CGTGCTGTCG TACCTGTGCG

851 ACAACTTCTG CCCGGCCATC AAGAAGTACG AGGGTGGGGT CGACGCCACC

901 ACCCGGTTCA TCCTGGACAA CCCCGGGTTC GTCACCTTCG GCTGGTACCG

951 TCTCAAACCG GGCCGGAACA ACACGCTAGC CCAGCCGCGG GCCCCGATGG

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1151 CCGGGCACCC GGAGGACCTG GTTATTCAGA TATCCTGTCT GCTCTACGAC

1201 CTGTCCACCA CCGCCCTGGA GCACGTCCTC CTGTTTTCGC TCGGTTCCTG

1251 CGACCTCCCC GAATCCCACC TGAACGAGCT GGCGGCCAGG GGCCTGCCCA

1301 CGCCCGTGGT TCTGGAATTC GACAGCGAAT TCGAGATGCT GTTGGCCTTC

1351 ATGACCCTTG TGAAACAGTA CGGCCCCGAG TTCGTGACCG GGTACAACAT

1401 CATCAACTTC GACTGGCCCT TCTTGCTGGC CAAGTTGACG GACATTTACA

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1551 GAACGGCATG GTGAACATCG ACATGTACGG GATCATAACC GACAAGATCA

1601 AGCTCTCGAG CTACAAGCTC AACGCCGTGG CCGAAGCCGT CCTGAAGGAC

1651 AAGAAGAAGG ACCTGAGCTA TCGCGACATC CCCGCCTACT ACGCCGCCGG

1701 GCCCGCGCAA CGCGGGGTGA TCGGCGAGTA CTGCATACAG GATTCCCTGC

1751 TGGTGGGCCA GCTGTTTTTT AAGTTTTTGC CCCATCTGGA GCTCTCGGCC

1801 GTCGCGCGCT TGGCGGGTAT TAACATCACC CGCACCATCT ACGACGGCCA

1851 GCAGATCCGC GTCTTTACGT GCCTGCTGCG CCTGGCCGAC CAGAAGGGCT

1901 TTATTCTGCC GGACACCCAG GGGCGATTTA GGGGCGCCGG GGGGGAGGCG

1951 CCCAAGCGTC CGGCCGCAGC CCGGGAGGAC GAGGAGCGGC CAGAGGAGGA

2001 GGGGGAGGAC GAGGACGAAC GCGAGGAGGG CGGGGGCGAG CGGGAGCCGG

2051 AGGGCGCGCG GGAGACCGCC GGCCGGCACG TGGGGTACCA GGGGGCCAGG

2101 GTCCTTGACC CCACTTCCGG GTTTCACGTG AACCCCGTGG TGGTGTTCGA

2151 CTTTGCCAGC CTGTACCCCA GCATCATCCA GGCCCACAAC CTGTGCTTCA

2201 GCACGCTCTC CCTGAGGGCC GACGCAGTGG CGCACCTGGA GGCGGGCAAG

2251 GACTACCTGG AGATCGAGGT GGGGGGGCGA CGGCTGTTCT TCGTCAAGGC

2301 TCACGTGCGA GAGAGCCTCC TCAGCATCCT CCTGCGGGAC TGGCTCGCCA

2351 TGCGAAAGCA GATCCGCTCG CGGATTCCCC AGAGCAGCCC CGAGGAGGCC

2401 GTGCTCCTGG ACAAGCAGCA GGCCGCCATC AAGGTCGTGT GTAACTCGGT

2451 GTACGGGTTC ACGGGAGCGC AGCACGGACT CCTGCCGTGC CTGCACGTTG

2501 CCGCGACGGT GACGACCATC GGCCGCGAGA TGCTGCTCGC GACCCGCGAG

2551 TACGTCCACG CGCGCTGGGC GGCCTTCGAA CAGCTCCTGG CCGATTTCCC

2601 GGAGGCGGCC GACATGCGCG CCCCCGGGCC CTATTCCATG CGCATCATCT

2651 ACGGGGACAC GGACTCCATA TTTGTGCTGT GCCGCGGCCT CACGGCCGCC

2701 GGGCTGACGG CCATGGGCGA CAAGATGGCG AGCCACATCT CGCGCGCGCT

2751 GTTTCTGCCC CCCATCAAAC TCGAGTGCGA AAAGACGTTC ACCAAGCTGC

2801 TGCTGATCGC CAAGAAAAAG TACATCGGCG TCATCTACGG GGGTAAGATG

2851 CTCATCAAGG GCGTGGATCT GGTGCGCAAA AACAACTGCG CGTTTATCAA

2901 CCGCACCTCC AGGGCCCTGG TCGACCTGCT GTTTTACGAC GATACCGTAT

2951 CCGGAGCGGC CGCCGCGTTA GCCGAGCGCC CCGCAGAGGA GTGGCTGGCG

3001 CGACCCCTGC CCGAGGGACT GCAGGCGTTC GGGGCCGTCC TCGTAGACGC

3051 CCATCGGCGC ATCACCGACC CGGAGAGGGA CATCCAGGAC TTTGTCCTCA

3101 CCGCCGAACT GAGCAGACAC CCGCGCGCGT ACACCAACAA GCGCCTGGCC

3151 CACCTGACGG TGTATTACAA GCTCATGGCC CGCCGCGCGC AGGTCCCGTC

3201 CATCAAGGAC CGGATCCCGT ACGTGATCGT GGCCCAGACC CGCGAGGTAG

3251 AGGAGACGGT CGCGCGGCTG GCCGCCCTCC GCGAGCTAGA CGCCGCCGCC

3301 CCAGGGGACG AGCCCGCCCC CCCCGCGGCC CTGCCCTCCC CGGCCAAGCG

3351 CCCCCGGGAG ACGCCGTCGC ATGCCGACCC CCCGGGAGGC GCGTCCAAGC

3401 CCCGCAAGCT GCTGGTGTCC GAGCTGGCCG AGGATCCCGC ATACGCCATT

3451 GCCCACGGCG TCGCCCTGAA CACGGACTAT TACTTCTCCC ACCTGTTGGG

3501 GGCGGCGTGC GTGACATTCA AGGCCCTGTT TGGGAATAAC GCCAAGATCA

3551 CCGAGAGTCT GTTAAAAAGG TTTATTCCCG AAGTGTGGCA CCCCCCGGAC

3601 GACGTGGCCG CGCGGCTCCG GGCCGCAGGG TTCGGGGCGG TGGGTGCCGG

3651 CGCTACGGCG GAGGAAACTC GTCGAATGTT GCATAGAGCC TTTGATACTC

3701 TAGCATGA

SEQ.ID.NO. 6 Amino acid sequence of DNA polymerase for HSV1-KOS-M1

1 MFSGGGGPLS PGGKSAARAA SGFFAPAGPR GAGRGPPPCL RQNFYNPYLA

51 PVGTQQKPTG PTQRHTYYSE CDEFRFIAPR VLDEDAPPEK RAGVHDGHLK

101 RAPKVYCGGD ERDVLRVGSG GFWPRRSRLW GGVDHAPAGF NPTVTVFHVY

151 DILENVEHAY GMRAAQFHAR FMDAITPTGT VITLLGLTPE GHRVAVHVYG

201 TRQYFYMNKE EVDRHLQCRA PRDLCERMAA ALRESPGASF RGISADHFEA

251 EVVERTDVYY YETRPALFYR VYVRSGRVLS YLCDNFCPAI KKYEGGVDAT

301 TRFILDNPGF VTFGWYRLKP GRNNTLAQPR APMAFGTSSD VEFNCTADNL

351 AIEGGMSDLP AYKLMCFDIE CKAGGEDELA FPVAGHPEDL VIQISCLLYD

401 LSTTALEHVL LFSLGSCDLP ESHLNELAAR GLPTPVVLEF DSEFEMLLAF

451 MTLVKQYGPE FVTGYNIINF DWPFLLAKLT DIYKVPLDGY GRMNGRGVFR

501 VWDIGQSHFQ KRSKIKVNGM VNIDMYGIIT DKIKLSSYKL NAVAEAVLKD

551 KKKDLSYRDI PAYYAAGPAQ RGVIGEYCIQ DSLLVGQLFF KFLPHLELSA

601 VARLAGINIT RTIYDGQQIR VFTCLLRLAD QKGFILPDTQ GRFRGAGGEA

651 PKRPAAARED EERPEEEGED EDEREEGGGE REPEGARETA GRHVGYQGAR

701 VLDPTSGFHV NPVVVFDFAS LYPSIIQAHN LCFSTLSLRA DAVAHLEAGK

751 DYLEIEVGGR RLFFVKAHVR ESLLSILLRD WLAMRKQIRS RIPQSSPEEA

801 VLLDKQQAAI KVVCNSVYGF TGAQHGLLPC LHVAATVTTI GREMLLATRE

851 YVHARWAAFE QLLADFPEAA DMRAPGPYSM RIIYGDTDSI FVLCRGLTAA

901 GLTAMGDKMA SHISRALFLP PIKLECEKTF TKLLLIAKKK YIGVIYGGKM

951 LIKGVDLVRK NNCAFINRTS RALVDLLFYD DTVSGAAAAL AERPAEEWLA

1001 RPLPEGLQAF GAVLVDAHRR ITDPERDIQD FVLTAELSRH PRAYTNKRLA

1051 HLTVYYKLMA RRAQVPSIKD RIPYVIVAQT REVEETVARL AALRELDAAA

1101 PGDEPAPPAA LPSPAKRPRE TPSHADPPGG ASKPRKLLVS ELAEDPAYAI

1151 AHGVALNTDY YFSHLLGAAC VTFKALFGNN AKITESLLKR FIPEVWHPPD

1201 DVAARLRAAG FGAVGAGATA EETRRMLHRA FDTLA*

SEQ.ID.NO. 7 DNA sequence of HSV polymerase gene for HSV1-F-M1

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   1 ATGTTTTCCG GTGGCGGCGG CCCGCTGTCC CCCGGAGGAA AGTCGGCGGC
  51 CAGGGCGGCG TCCGGGTTTT TTGCGCCCGC CGGCCCTCGC GGAGCCGGCC
 101 GGGGACCCCC GCCTTGCTTG AGGCAAAACT TTTACAACCC CTACCTCGCC
 151 CCAGTCGGGA CGCAACAGAA GCCGACCGGG CCAACCCAGC GCCATACGTA
 201 CTATAGCGAA TGCGATGAAT TTCGATTCAT CGCCCCGCGG GTGCTGGACG
 251 AGGATGCCCC CCCGGAGAAG CGCGCCGGGG TGCACGACGG TCACCTCAAG
 301 CGCGCCCCCA AGGTGTACTG CGGGGGGGAC GAGCGCGACG TCCTCCGCGT
 351 CGGGTCGGGC GGCTTCTGGC CGCGGCGCTC GCGCCTGTGG GGCGGCGTGG
 401 ACCACGCCCC GGCGGGGTTC AACCCCACCG TCACCGTCTT TCACGTGTAC
 451 GACATCCTGG AGAACGTGGA GCACGCGTAC GGCATGCGCG CGGCCCAGTT
 501 CCACGCGCGG TTTATGGACG CCATCACACC GACGGGGACC GTCATCACGC
 551 TCCTGGGCCT GACTCCGGAA GGCCACCGGG TGGCCGTTCA CGTTTACGGC
 601 ACGCGGCAGT ACTTTTACAT GAACAAGGAG GAGGTCGACA GGCACCTACA
 651 ATGCCGCGCC CCACGAGATC TCTGCGAGCG CATGGCCGCG GCCCTGCGCG
 701 AGTCCCCGGG CGCGTCGTTC CGCGGCATTT CCGCGGACCA CTTCGAGGCG
 751 GAGGTGGTGG AGCGCACCGA CGTGTACTAC TACGAGACGC GCCCCGCTCT
 801 GTTTTACCGC GTCTACGTCC GAAGCGGGCG CGTGCTGTCG TACCTGTGCG
 851 ACAACTTCTG CCCGGCCATC AAGAAGTACG AGGGTGGGGT CGACGCCACC
 901 ACCCGGTTCA TCCTGGACAA CCCCGGGTTC GTCACCTTCG GCTGGTACCG
 951 TCTCAAACCG GGCCGGAACA ACACGCTAGC CCAGCCGCGG GCCCCGATGG
1001 CCTTCGGGAC ATCCAGCGAC GTCGAGTTTA ACTGTACGGC GGACAACCTG
1051 GCCATCGAGG GGGGCATGAG CGACCTACCG GCATACAAGC TCATGTGCTT
1101 CGATATCGAA TGCAAGGCGG GGGGGGAGGA CGAGCTGGCC TTTCCGGTGG
1151 CCGGGCACCC GGAGGACCTG GTCATCCAGA TATCCTGTCT GCTCTACGAC
1201 CTGTCCACCA CCGCCCTGGA GCACGTCCTC CTGTTTTCGC TCGGTTCCTG
1251 CGACCTCCCC GAATCCCACC TGAACGAGCT GGCGGCCAGG GGCCTGCCCA
1301 CGCCCGTGGT TCTGGAATTC GACAGCGAAT TCGAGATGCT GTTGGCCTTC
1351 ATGACCCTTG TGAAACAGTA CGGCCCCGAG TTCGTGACCG GGTACAACAT
1401 CATCAACTTC GACTGGCCCT TCTTGCTGGC CAAGCTGACG GACATTTACA
1451 AGGTCCCCCT GGACGGGTAC GGCCGCATGA ACGGCCGGGG CGTGTTTCGC
1501 GTGTGGGACA TAGGCCAGAG CCACTTCCAG AAGCGCAGCA AGATAAAGGT
1551 GAACGGCATG GTGAACATCG ACATGTACGG GATTATAACC GACAAGATCA
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1601 AGCTCTCGAG CTACAAGCTC AACGCCGTGG CCGAAGCCGT CCTGAAGGAC

1651 AAGAAGAAGG ACCTGAGCTA TCGCGACATC CCCGCCTACT ACGCCGCCGG

1701 GCCCGCGCAA CGCGGGGTGA TCGGCGAGTA CTGCATACAG GATTCCCTGC

1751 TGGTGGGCCA GCTGTTTTTT AAGTTTTTGC CCCATCTGGA GCTCTCGGCC

1801 GTCGCGCGCT TGGCGGGTAT TAACATCACC CGCACCATCT ACGACGGCCA

1851 GCAGATCCGC GTCTTTACGT GCCTGCTGCG CCTGGCCGAC CAGAAGGGCT

1901 TTATTCTGCC GGACACCCAG GGGCGATTTA GGGGCGGCGG GGGGGAGGCG

1951 CCCAAGCGTC CGGCCGCAGC CCGGGAGGAC GAGGAGCGGC CAGAGGAGGA

2001 GGGGGAGGAC GAGGACGAAC GCGAGGAGGG CGGGGGCGAG CGGGAGCCGG

2051 AGGGCGCGCG GGAGACCGCC GGCCGGCACG TGGGGTACCA GGGGGCCAGG

2101 GTCCTTGACC CCACTTCCGG GTTTCATGTG AACCCCGTGG TGGTGTTCGA

2151 CTTTGCCAGC CTGTACCCCA GCATCATCCA GGCCCACAAC CTGTGCTTCA

2201 GCACGCTCTC CCTGAGGGCC GACGCAGTGG CGCACCTGGA GGCGGGCAAG

2251 GACTACCTGG AGATCGAGGT GGGGGGGCGA CGGCTGTTCT TCGTCAAGGC

2301 TCACGTGCGA GAGAGCCTCC TCAGCATCCT CCTGCGGGAC TGGCTCGCCA

2351 TGCGAAAGCA GATCCGCTCG CGGATTCCCC AGAGCAGCCC CGAGGAGGCC

2401 GTGCTCCTGG ACAAGCAGCA GGCCGCCATC AAGGTCGTGT GTAACTCGGT

2451 TTACGGGTTC ACGGGAGCGC AGCACGGACT CCTGCCGTGC CTGCACGTTG

2501 CCGCGACGGT GACGACCATC GGCCGCGAGA TGCTGCTCGC GACCCGCGAG

2551 TACGTCCACG CGCGCTGGGC GGCCTTCGAA CAGCTCCTGG CCGATTTCCC

2601 GGAGGCGGCC GACATGCGCG CCCCCGGGCC CTATTCCATG CGCATCATCT

2651 ACGGGGACAC GGACTCCATC TTTGTGCTGT GCCGCGGCCT CACGGCCGCC

2701 GGGCTGACGG CCGTGGGCGA CAAGATGGCG AGCCACATCT CGCGCGCGCT

2751 GTTTCTGTCC CCCATCAAAC TCGAGTGCGA AAAGACGTTC ACCAAGCTGC

2801 TGCTGATCGC CAAGAAAAAG TACATCGGCG TCATCTACGG GGGTAAGATG

2851 CTCATCAAGG GCGTGGATCT GGTGCGCAAA AACAACTGCG CGTTTATCAA

2901 CCGCACCTCC AGGGCCCTGG TCGACCTGCT GTTTTACGAC GATACCGTAT

2951 CCGGAGCGGC CGCCGCGTTA GCCGAGCGCC CCGCAGAGGA GTGGCTGGCG

3001 CGACCCCTGC CCGAGGGACT GCAGGCGTTC GGGGCCGTCC TCGTAGACGC

3051 CCATCGGCGC ATCACCGACC CGGAGAGGGA CATCCAGGAC TTTGTCCTCA

3101 CCGCCGAACT GAGCAGACAC CCGCGCGCGT ACACCAACAA GCGCCTGGCC

3151 CACCTGACGG TGTATTACAA GCTCATGGCC CGCCGCGCGC AGGTCCCGTC

3201 CATCAAGGAC CGGATCCCGT ACGTGATCGT GGCCCAGACC CGCGAGGTAG

3251 AGGAGACGGT CGCGCGGCTG GCCGCCCTCC GCGAGCTCGA CGCCGCCGCC

3301 CCAGGGGACG AGCCCGCCCC CCCCGCGGCC CTGCCCTCCC CGGCCAAGCG

3351 CCCCCGGGAG ACGCCGTTGC ATGCCGACCC CCCGGGAGGC GCGTCCAAGC

3401 CCCGCAAGCT GCTGGTGTCC GAGCTGGCCG AGGATCCCGC ATACGCCATT

3451 GCCCACGGCG TCGCCCTGAA CACGGACTAT TACTTCTCCC ACCTGTTGGG

3501 GGCGGCGTGC GTGACATTCA AGGCCCTGTT TGGGAATAAC GCCAAGATCA

3551 CCGAGAGTCT GTTAAAAAGG TTTATTCCCG AAGTGTGGCA CCCCCCGGAC

3601 GACGTGGCCG CGCGGCTCCG GGCCGCAGGG TTCGGGGCGG TGGGTGCCGG

3651 CGCTACGGCG GAGGAAACTC GTCGAATGTT GCATAGAGCC TTTGATACTC

3701 TAGCATGA

SEQ.ID.NO. 8 Amino acid sequence of DNA polymerase for HSV1-F-M1

1 MFSGGGGPLS PGGKSAARAA SGFFAPAGPR GAGRGPPPCL RQNFYNPYLA

51 PVGTQQKPTG PTQRHTYYSE CDEFRFIAPR VLDEDAPPEK RAGVHDGHLK

101 RAPKVYCGGD ERDVLRVGSG GFWPRRSRLW GGVDHAPAGF NPTVTVFHVY

151 DILENVEHAY GMRAAQFHAR FMDAITPTGT VITLLGLTPE GHRVAVHVYG

201 TRQYFYMNKE EVDRHLQCRA PRDLCERMAA ALRESPGASF RGISADHFEA

251 EVVERTDVYY YETRPALFYR VYVRSGRVLS YLCDNFCPAI KKYEGGVDAT

301 TRFILDNPGF VTFGWYRLKP GRNNTLAQPR APMAFGTSSD VEFNCTADNL

351 AIEGGMSDLP AYKLMCFDIE CKAGGEDELA FPVAGHPEDL VIQISCLLYD

401 LSTTALEHVL LFSLGSCDLP ESHLNELAAR GLPTPVVLEF DSEFEMLLAF

451 MTLVKQYGPE FVTGYNIINF DWPFLLAKLT DIYKVPLDGY GRMNGRGVFR

501 VWDIGQSHFQ KRSKIKVNGM VNIDMYGIIT DKIKLSSYKL NAVAEAVLKD

551 KKKDLSYRDI PAYYAAGPAQ RGVIGEYCIQ DSLLVGQLFF KFLPHLELSA

601 VARLAGINIT RTIYDGQQIR VFTCLLRLAD QKGFILPDTQ GRFRGGGGEA

651 PKRPAAARED EERPEEEGED EDEREEGGGE REPEGARETA GRHVGYQGAR

701 VLDPTSGFHV NPVVVFDFAS LYPSIIQAHN LCFSTLSLRA DAVAHLEAGK

751 DYLEIEVGGR RLFFVKAHVR ESLLSILLRD WLAMRKQIRS RIPQSSPEEA

801 VLLDKQQAAI KVVCNSVYGF TGAQHGLLPC LHVAATVTTI GREMLLATRE

851 YVHARWAAFE QLLADFPEAA DMRAPGPYSM RIIYGDTDSI FVLCRGLTAA

901 GLTAVGDKMA SHISRALFLS PIKLECEKTF TKLLLIAKKK YIGVIYGGKM

951 LIKGVDLVRK NNCAFINRTS RALVDLLFYD DTVSGAAAAL AERPAEEWLA

1001 RPLPEGLQAF GAVLVDAHRR ITDPERDIQD FVLTAELSRH PRAYTNKRLA

1051 HLTVYYKLMA RRAQVPSIKD RIPYVIVAQT REVEETVARL AALRELDAAA

1101 PGDEPAPPAA LPSPAKRPRE TPLHADPPGG ASKPRKLLVS ELAEDPAYAI

1151 AHGVALNTDY YFSHLLGAAC VTFKALFGNN AKITESLLKR FIPEVWHPPD

1201 DVAARLRAAG FGAVGAGATA EETRRMLHRA FDTLA*

SEQ.ID.NO. 9 DNA sequence of HSV polymerase gene for HSV1-DJL-M1

1 ATGTTTTCCG GTGGCGGCGG CCCGCTGTCC CCCGGAGGAA AGTCGGCGGC

51 CAGGGCGGCG TCCGGGTTTT TTGCGCCCGC CGGCCCTCGC GGAGCCGGCC

101 GGGGACCCCC GCCTTGTTTG AGGCAAAACT TTTACAACCC CTACCTCGCC

151 CCAGTCGGGA CGCAACAGAA GCCGACCGGG CCAACCCAGC GCCATACGTA

201 CTATAGCGAA TGCGATGAAT TTCGATTCAT CGCCCCGCGG GTGCTGGACG

251 AGGATGCCCC CCCGGAGAAG CGCGCCGGGG TGCACGACGG TCACCTCAAG

301 CGCGCCCCCA AGGTGTACTG CGGGGGGGAC GAGCGCGACG TCCTCCGCGT

351 CGGGTCGGGC GGCTTCTGGC CGCGGCGCTC GCGCCTGTGG GGCGGCGTGG

401 ACCACGCCCC GGCGGGGTTC AACCCCACCG TCACCGTCTT TCACGTGTAT

451 GACATCCTGG AGAACGTGGA GCACGCGTAC GGCATGCGCG CGGCCCAGTT

501 CCACGCGCGG TTTATGGACG CCATCACACC GACGGGGACC GTCATCACGC

551 TCCTGGGCCT GACTCCGGAA GGCCACCGGG TGGCCGTTCA CGTTTACGGC

601 ACGCGGCAGT ACTTTTACAT GAACAAGGAG GAGGTTGACA GGCACCTACA

651 ATGCCGCGCC CCACGAGATC TCTGCGAGCG CATGGCCGCG GCCCTGCGCG

701 AGTCCCCGGG CGCGTCGTTC CGCGGCATCT CCGCGGACCA CTTCGAGGCG

751 GAGGTGGTGG AGCGCACCGA CGTGTACTAC TACGAGACGC GCCCCGCTCT

801 GTTTTACCGC GTCTACGTCC GAAGCGGGCG CGTGCTGTCG TACCTGTGCG

851 ACAACTTCTG CCCGGCCATC AAGAAGTACG AGGGTGGGGT CGACGCCACC

901 ACCCGGTTCA TCCTGGACAA CCCCGGGTTC GTCACCTTCG GCTGGTACCG

951 TCTCAAACCG GGCCGGAACA ACACGCTAGC CCAGCCGCGG GCCCCGATGG

1001 CCTTCGGGAC ATCCAGCGAT GTCGAGTTTA ACTGTACGGC GGACAACCTG

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1201 CTGTCCACCA CCGCCCTGGA GCACGTCCTC CTGTTTTCGC TCGGTTCCTG

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2051 AGGGCGCGCG GGAGACCGCC GGCCGGCACG TGGGGTACCA GGGGGCCAGG

2101 GTCCTTGACC CCACTTCCGG GTTTCACGTG AACCCCGTGG TGGTGTTCGA

2151 CTTTGCCAGC CTGTACCCCA GCATCATCCA GGCCCACAAC CTGTGCTTCA

2201 GCACGCTCTC CCTGAGGGCC GACGCAGTGG CGCACCTGGA GGCGGGCAAG

2251 GACTACCTGG AGATCGAGGT GGGGGGGCGA CGGCTGTTCT TCGTCAAGGC

2301 TCACGTGCGA GAGAGCCTCC TCAGCATCCT CCTGCGGGAC TGGCTCGCCA

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2401 GTGCTCCTGG ACAAGCAGCA GGCCGCCATC AAGGTCGTGT GTAACTCGGT

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2651 ACGGGGACAC GGACTCCATA TTTGTGCTGT GCCGCGGCCT CACGGCCGCC

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3151 CACCTGACGG TGTATTACAA GCTCATGGCC CGCCGCGCGC AGGTCCCGTC

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3251 AGGAGACGGT CGCGCGGCTG GCCGCCCTCC GCGAGCTAGA CGCCGCCGCC

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3351 CCCCCGGGAG ACGCCGTCGC CTGCCGACCC CCCGGGAGGC GCGTCCAAGC

3401 CCCGCAAGCT GCTGGTGTCC GAGCTGGCCG AGGATCCCGC ATACGCCATT

3451 GCCCACGGCG TCGCCCTGAA CACGGACTAT TACTTCTCCC ACCTGTTGGG

3501 GGCGGCGTGC GTGACATTCA AGGCCCTGTT TGGGAATAAC GCCAAGATCA

3551 CCGAGAGTCT GTTAAAAAGG TTTATTCCCG AAGTGTGGCA CCCCCCGGAC

3601 GACGTGGCCG CGCGGCTCCG GACCGCAGGG TTCGGGGCGG TGGGTGCCGG

3651 CGCTACGGCG GAGGAAACTC GTCGAATGTT GCATAGAGCC TTTGATACTC

3701 TAGCATGA

SEQ.ID.NO. 10 Amino acid sequence of DNA polymerase for HSV1-DJL-M1

1 MFSGGGGPLS PGGKSAARAA SGFFAPAGPR GAGRGPPPCL RQNFYNPYLA

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101 RAPKVYCGGD ERDVLRVGSG GFWPRRSRLW GGVDHAPAGF NPTVTVFHVY

151 DILENVEHAY GMRAAQFHAR FMDAITPTGT VITLLGLTPE GHRVAVHVYG

201 TRQYFYMNKE EVDRHLQCRA PRDLCERMAA ALRESPGASF RGISADHFEA

251 EVVERTDVYY YETRPALFYR VYVRSGRVLS YLCDNFCPAI KKYEGGVDAT

301 TRFILDNPGF VTFGWYRLKP GRNNTLAQPR APMAFGTSSD VEFNCTADNL

351 AIEGGMSDLP AYKLMCFDIE CKAGGEDELA FPVAGHPEDL VIQISCLLYD

401 LSTTALEHVL LFSLGSCDLP ESHLNELAAR GLPTPVVLEF DSEFEMLLAF

451 MTLVKQYGPE FVTGYNIINF DWPFLLAKLT DIYKVPLDGY GRMNGRGVFR

501 VWDIGQSHFQ KRSKIKVNGM VNIDMYGIIT DKIKLSSYKL NAVAEAVLKD

551 KKKDLSYRDI PTYYAAGPAQ RGVIGEYCIQ DSLLVGQLFF KFLPHLELSA

601 VARLAGINIT RTIYDGQQIR VFTCLLRLAD QKGFILPDTQ GRFRGAGGEA

651 PKRPAAARED EERPEEEGED ENEREEGGGE REPEGARETA GRHVGYQGAR

701 VLDPTSGFHV NPVVVFDFAS LYPSIIQAHN LCFSTLSLRA DAVAHLEAGK

751 DYLEIEVGGR RLFFVKAHVR ESLLSILLRD WLAMRKQIRS RIPQSSPEEA

801 VLLDKQQAAI KVVCNSVYGF TGAQHGLLPC LHVAATVTTI GREMLLATRE

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951 LIKGVDLVRK NNCAFINRTS RALVDLLFYD DTVSGAAAAL AERPAEEWLA

1001 RPLPEGLQAF GAVLVDAHRR ITDPERDIQD FVLTAELSRH PRAYTNKRLA

1051 HLTVYYKLMA RRAQVPSIKD RIPYVIVAQT REVEETVARL AALRELDAAA

1101 PGDEPAPPAA LPSPAKRPRE TPSPADPPGG ASKPRKLLVS ELAEDPAYAI

1151 AHGVALNTDY YFSHLLGAAC VTFKALFGNN AKITESLLKR FIPEVWHPPD

1201 DVAARLRTAG FGAVGAGATA EETRRMLHRA FDTLA*

SEQ.ID.NO. 11 DNA sequence of DNA polymerase gene for HMCV-AD169-M1

1 ATGTTTTTCA ACCCGTATCT GAGCGGCGGC GTGACCGGCG GTGCGGTCGC

51 GGGTGGCCGG CGTCAGCGTT CGCAGCCCGG CTCCGCGCAG GGCTCGGGCA

101 AGCGGCCGCC ACAGAAACAG TTTTTGCAGA TCGTGCCGCG AGGTGTCATG

151 TTCGACGGTC AGACGGGGTT GATCAAGCAT AAGACGGGAC GGCTGCCTCT

201 CATGTTCTAT CGAGAGATTA AACATTTGTT GAGTCATGAC ATGGTTTGGC

251 CGTGTCCTTG GCGCGAGACC CTGGTGGGTC GCGTGGTGGG ACCTATTCGT

301 TTTCACACCT ACGATCAGAC GGACGCCGTG CTCTTCTTCG ACTCGCCCGA

351 AAACGTGTCG CCGCGCTATC GTCAGCATCT GGTGCCTTCG GGGAACGTGT

401 TGCGTTTCTT CGGGGCCACA GAACACGGCT ACAGTATCTG CGTCAACGTT

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501 GCGTGAGGTC ATTGCCAGCG TGGGCGAACT AGTGCCCGAA CCGCGGACGC

551 CATACGCCGT GTCTGTCACG CCGGCCACCA AGACCTCCAT CTATGGGTAC

601 GGGACGCGAC CCGTGCCCGA TTTGCAGTGT GTGTCTATCA GCAACTGGAC

651 CATGGCCAGA AAAATCGGCG AGTATCTGCT GGAGCAGGGT TTTCCCGTGT

701 ACGAGGTCCG TGTGGATCCG CTGACGCGTT TGGTCATCGA TCGGCGGATC

751 ACCACGTTCG GCTGGTGCTC CGTGAATCGT TACGACTGGC GGCAGCAGGG

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901 GATATCGAGT GCATGAGCGG CGAGGGTGGT TTTCCCTGCG CCGAGAAGTC

951 CGATGACATT GTCATTCAGA TCTCGTGCGT GTGCTACGAG ACGGGGGGAA

1001 ACACCGCCGT GGATCAGGGG ATCCCAAACG GGAACGATGG TCGGGGCTGC

1051 ACTTCGGAGG GTGTGATCTT TGGGCACTCG GGTCTTCATC TCTTTACGAT

1101 CGGCACCTGC GGGCAGGTGG GCCCAGACGT GGACGTCTAC GAGTTCCCTT

1151 CCGAATACGA GCTGCTGCTG GGCTTTATGC TTTTCTTTCA ACGGTACGCG

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1351 GGTTTTAAGC GGCAGTACGC CGCCGCTTTT CCCTCGGCTT CTCACAACAA

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1451 TCGACATGTA CCCTGTATGC ATGGCCAAGA CTAACTCGCC CAACTATAAG

1501 CTCAACACTA TGGCCGAGCT TTACCTGCGG CAACGCAAGG ATGACCTGTC

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1601 AGGTAGGCCG TTACTGTCTG CAGGACGCCG TATTGGTGCG CGATCTGTTC

1651 AACACCATTA ATTTTCACTA CGAGGCCGGG GCCATCGCGC GGCTGGCTAA

1701 AATTCCGTTG CGGCGTGTCA TCTTTGACGG ACAGCAGATC CGTATCTACA

1751 CCTCGCTGCT GGACGAGTGC GCCTGCCGCG ATTTTATCCT GCCCAACCAC

1801 TACAGCAAAG GTACGACGGT GCCCGAAACG AATAGCGTTG CTGTGTCACC

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2201 CCACCCTGCT GGTGCCGGGT GGCGAGTACC CTGTGGACCC CGCCGACGTA

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2451 CTACGGTTTT ACCGGCGCGC TGAACGGTAT GATGCCGTGT CTGCCCATCG

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2601 TCAGGAAGAC TATGTAGTGG GAACGCGGGA GGGGGATTCG GAGGAGAGCA

2651 GCGCGTTACC GGAGGGGCTC GAAACATCGT CAGGGGGCTC GAACGAACGG

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3451 GGAGAGCCGG CAAAGAAGAG GGCGCGGAAA CCACCGTCGG CCGTGTGCAA

3501 CTACGAGGTA GCCGAAGATC CGAGCTACGT GCGCGAGCAC GGCGTGCCCA

3551 TTCACGCCGA CAAGTACTTT GAGCAGGTTC TCAAGGCTGT AACTAACGTG

3601 CTGTCGCCCG TCTTTCCCGG CGGCGAAACC GCGCGCAAGG ACAAGTTTTT

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SEQ.ID.NO.12 Amino acid sequence of DNA polymerase for HCMV-AD169-M1

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201 GTRPVPDLQC VSISNWTMAR KIGEYLLEQG FPVYEVRVDP LTRLVIDRRI

251 TTFGWCSVNR YDWRQQGRAS TCDIEVDCDV SDLVAVPDDS SWPRYRCLSF

301 DIECMSGEGG FPCAEKSDDI VIQISCVCYE TGGNTAVDQG IPNGNDGRGC

351 TSEGVIFGHS GLHLFTIGTC GQVGPDVDVY EFPSEYELLL GFMLFFQRYA

401 PAFVTGYNIN SFDLKYILTR LEYLYKVDSQ RFCKLPTAQG GRFFLHSPAV

451 GFKRQYAAAF PSASHNNPAS TAATKVYIAG SVVIDMYPVC MAKTNSPNYK

501 LNTMAELYLR QRKDDLSYKD IPRCFVANAE GRAQVGRYCL QDAVLVRDLF

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601 YSKGTTVPET NSVAVSPNAA IISTAAVPGD AGSVAAMFQM SPPLQSAPSS

651 QDGVSPGSGS NSSSSVGVFS VGSGSSGGVG VSNDNHGAGG TAAVSYQGAT

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901 RVEARVIYGD TDSVFVRFRG LTPQALVARG PSLAHYVTAC LFVEPVKLEF

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Figure 6
SEQ.ID.NO.13 Amino acid sequence of DNA polymerase for HCMV-AD169

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1201 LSPVFPGGET ARKDKFLHMV LPRRLHLEPA FLPYSVKAHE CC*

SEQUENCE LISTING

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Hopkins, Todd
Thomsen, Darrell

<120> A Method for Treating Herpes Virus

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Val Glu Gly Ala Met Cys Asp Leu Pro Ala Tyr Lys Leu Met Cys Phe
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Thr Gln Thr Ala Pro Pro Pro Cys Arg Arg Gln Asn Phe Tyr Asn Pro
35 40 45

His Leu Ala Gln Thr Gly Thr Gln Pro Lys Ala Pro Gly Pro Ala Gln
50 55 60

Arg His Thr Tyr Tyr Ser Glu Cys Asp Glu Phe Arg Phe Ile Ala Pro
65 70 75 80

Arg Ser Leu Asp Glu Asp Ala Pro Ala Glu Gln Arg Thr Gly Val His
85 90 95

Asp Gly Arg Leu Arg Arg Ala Pro Lys Val Tyr Cys Gly Gly Asp Glu
100 105 110

Arg Asp Val Leu Arg Val Gly Pro Glu Gly Phe Trp Pro Arg Arg Leu
115 120 125

Arg Leu Trp Gly Gly Ala Asp His Ala Pro Glu Gly Phe Asp Pro Thr
130 135 140

Val Thr Val Phe His Val Tyr Asp Ile Leu Glu His Val Glu His Ala

```
145                 150                 155                 160

Tyr Ser Met Arg Ala Ala Gln Leu His Glu Arg Phe Met Asp Ala Ile
                165                 170                 175

Thr Pro Ala Gly Thr Val Ile Thr Leu Leu Gly Leu Thr Pro Glu Gly
            180                 185                 190

His Arg Val Ala Val His Val Tyr Gly Thr Arg Gln Tyr Phe Tyr Met
        195                 200                 205

Asn Lys Ala Glu Val Asp Arg His Leu Gln Cys Arg Ala Pro Arg Asp
    210                 215                 220

Leu Cys Glu Arg Leu Ala Ala Ala Leu Arg Glu Ser Pro Gly Ala Ser
225                 230                 235                 240

Phe Arg Gly Ile Ser Ala Asp His Phe Glu Ala Glu Val Val Glu Arg
                245                 250                 255

Ala Asp Val Tyr Tyr Tyr Glu Thr Arg Pro Thr Leu Tyr Tyr Arg Val
            260                 265                 270

Phe Val Arg Ser Gly Arg Ala Leu Ala Tyr Leu Cys Asp Asn Phe Cys
        275                 280                 285

Pro Ala Ile Arg Lys Tyr Glu Gly Gly Val Asp Ala Thr Thr Arg Phe
    290                 295                 300

Ile Leu Asp Asn Pro Gly Phe Val Thr Phe Gly Trp Tyr Arg Leu Lys
305                 310                 315                 320

Pro Gly Arg Gly Asn Ala Pro Ala Gln Pro Arg Pro Pro Thr Ala Phe
                325                 330                 335

Gly Thr Ser Ser Asp Val Glu Phe Asn Cys Thr Ala Asp Asn Leu Ala
            340                 345                 350

Val Glu Gly Ala Met Cys Asp Leu Pro Ala Tyr Lys Leu Met Cys Phe
        355                 360                 365

Asp Ile Glu Cys Lys Ala Gly Gly Glu Asp Glu Leu Ala Phe Pro Val
    370                 375                 380

Ala Glu Arg Pro Glu Asp Leu Val Ile Gln Ile Ser Cys Leu Leu Tyr
385                 390                 395                 400

Asp Leu Ser Thr Thr Ala Leu Glu His Ile Leu Leu Phe Ser Leu Gly
                405                 410                 415

Ser Cys Asp Leu Pro Glu Ser His Leu Ser Asp Leu Ala Ser Arg Gly
            420                 425                 430

Leu Pro Ala Pro Val Val Leu Glu Phe Asp Ser Glu Phe Glu Met Leu
        435                 440                 445

Leu Ala Phe Met Thr Phe Val Lys Gln Tyr Gly Pro Glu Phe Val Thr
    450                 455                 460

Gly Tyr Asn Ile Ile Asn Phe Asp Trp Pro Phe Val Leu Thr Lys Leu
465                 470                 475                 480
```

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Thr Glu Ile Tyr Lys Val Pro Leu Asp Gly Tyr Gly Arg Met Asn Gly
                485                 490                 495

Arg Gly Val Phe Arg Val Trp Asp Ile Gly Gln Ser His Phe Gln Lys
            500                 505                 510

Arg Ser Lys Ile Lys Val Asn Gly Met Val Asn Ile Asp Met Tyr Gly
        515                 520                 525

Ile Ile Thr Asp Lys Val Lys Leu Ser Ser Tyr Lys Leu Asn Ala Val
    530                 535                 540

Ala Glu Ala Val Leu Lys Asp Lys Lys Lys Asp Leu Ser Tyr Arg Asp
545                 550                 555                 560

Ile Pro Ala Tyr Tyr Ala Ser Gly Pro Ala Gln Arg Gly Val Ile Gly
                565                 570                 575

Glu Tyr Cys Val Gln Asp Ser Leu Leu Val Gly Gln Leu Phe Phe Lys
            580                 585                 590

Phe Leu Pro His Leu Glu Leu Ser Ala Val Ala Arg Leu Ala Gly Ile
        595                 600                 605

Asn Ile Thr Arg Thr Ile Tyr Asp Gly Gln Gln Ile Arg Val Phe Thr
    610                 615                 620

Cys Leu Leu Arg Leu Ala Gly Gln Lys Gly Phe Ile Leu Pro Asp Thr
625                 630                 635                 640

Gln Gly Arg Phe Arg Gly Leu Asp Lys Glu Ala Pro Lys Arg Pro Ala
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Val Pro Arg Gly Glu Gly Glu Arg Pro Gly Asp Gly Asn Gly Asp Glu
            660                 665                 670

Asp Lys Asp Asp Asp Glu Asp Gly Asp Glu Asp Gly Asp Glu Arg Glu
        675                 680                 685

Glu Val Ala Arg Glu Thr Gly Gly Arg His Val Gly Tyr Gln Gly Ala
    690                 695                 700

Arg Val Leu Asp Pro Thr Ser Gly Phe His Val Asp Pro Val Val Val
705                 710                 715                 720

Phe Asp Phe Ala Ser Leu Tyr Pro Ser Ile Ile Gln Ala His Asn Leu
                725                 730                 735

Cys Phe Ser Thr Leu Ser Leu Arg Pro Glu Ala Val Ala His Leu Glu
            740                 745                 750

Ala Asp Arg Asp Tyr Leu Glu Ile Glu Val Gly Gly Arg Arg Leu Phe
        755                 760                 765

Phe Val Lys Ala His Val Arg Glu Ser Leu Leu Ser Ile Leu Leu Arg
    770                 775                 780

Asp Trp Leu Ala Met Arg Lys Gln Ile Arg Ser Arg Ile Pro Gln Ser
785                 790                 795                 800

Pro Pro Glu Glu Ala Val Leu Leu Asp Lys Gln Gln Ala Ala Ile Lys
                805                 810                 815
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Val Val Cys Asn Ser Val Tyr Gly Phe Thr Gly Ala Gln His Gly Leu
            820                 825                 830

Leu Pro Cys Leu His Val Ala Ala Thr Val Thr Thr Ile Gly Arg Glu
        835                 840                 845

Met Leu Leu Ala Thr Arg Ala Tyr Val His Ala Arg Trp Ala Glu Phe
    850                 855                 860

Asp Gln Leu Leu Ala Asp Phe Pro Glu Ala Ala Gly Met Arg Ala Pro
865                 870                 875                 880

Gly Pro Tyr Ser Met Arg Ile Ile Tyr Gly Asp Thr Asp Ser Ile Phe
                885                 890                 895

Val Leu Cys Arg Gly Leu Thr Ala Ala Gly Leu Val Ala Met Gly Asp
            900                 905                 910

Lys Met Ala Ser His Ile Ser Arg Ala Leu Phe Leu Pro Pro Ile Lys
        915                 920                 925

Leu Glu Cys Glu Lys Thr Phe Thr Lys Leu Leu Leu Ile Ala Lys Lys
    930                 935                 940

Lys Tyr Ile Gly Val Ile Cys Gly Gly Lys Met Leu Ile Lys Gly Val
945                 950                 955                 960

Asp Leu Val Arg Lys Asn Asn Cys Ala Phe Ile Asn Arg Thr Ser Arg
                965                 970                 975

Ala Leu Val Asp Leu Leu Phe Tyr Asp Asp Thr Val Ser Gly Ala Ala
            980                 985                 990

Ala Ala Leu Ala Glu Arg Pro Ala  Glu Glu Trp Leu Ala  Arg Pro Leu
        995                 1000                1005

Pro Glu  Gly Leu Gln Ala Phe  Gly Ala Val Leu Val  Asp Ala His
    1010                1015                1020

Arg Arg  Ile Thr Asp Pro Glu  Arg Asp Ile Gln Asp  Phe Val Leu
    1025                1030                1035

Thr Ala  Glu Leu Ser Arg His  Pro Arg Ala Tyr Thr  Asn Lys Arg
    1040                1045                1050

Leu Ala  His Leu Thr Val Tyr  Tyr Lys Leu Met Ala  Arg Arg Ala
    1055                1060                1065

Gln Val  Pro Ser Ile Lys Asp  Arg Ile Pro Tyr Val  Ile Val Ala
    1070                1075                1080

Gln Thr  Arg Glu Val Glu Glu  Thr Val Ala Arg Leu  Ala Ala Leu
    1085                1090                1095

Arg Glu  Leu Asp Ala Ala Ala  Pro Gly Asp Glu Pro  Ala Pro Pro
    1100                1105                1110

Ala Ala  Leu Pro Ser Pro Ala  Lys Arg Pro Arg Glu  Thr Pro Ser
    1115                1120                1125

His Ala  Asp Pro Pro Gly Gly  Ala Ser Lys Pro Arg  Lys Leu Leu
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1130 1135 1140

Val Ser Glu Leu Ala Glu Asp Pro Gly Tyr Ala Ile Ala Arg Gly
1145 1150 1155

Val Pro Leu Asn Thr Asp Tyr Tyr Phe Ser His Leu Leu Gly Ala
1160 1165 1170

Ala Cys Val Thr Phe Lys Ala Leu Phe Gly Asn Asn Ala Lys Ile
1175 1180 1185

Thr Glu Ser Leu Leu Lys Arg Phe Ile Pro Glu Thr Trp His Pro
1190 1195 1200

Pro Asp Asp Val Ala Ala Arg Leu Arg Ala Ala Gly Phe Gly Pro
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Ala Gly Ala Gly Ala Thr Ala Glu Glu Thr Arg Arg Met Leu His
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Arg Ala Phe Asp Thr Leu Ala
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<400> 6

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Gly Arg Gly Pro Pro Pro Cys Leu Arg Gln Asn Phe Tyr Asn Pro Tyr
35 40 45

Leu Ala Pro Val Gly Thr Gln Gln Lys Pro Thr Gly Pro Thr Gln Arg
50 55 60

His Thr Tyr Tyr Ser Glu Cys Asp Glu Phe Arg Phe Ile Ala Pro Arg
65 70 75 80

Val Leu Asp Glu Asp Ala Pro Pro Glu Lys Arg Ala Gly Val His Asp
85 90 95

Gly His Leu Lys Arg Ala Pro Lys Val Tyr Cys Gly Gly Asp Glu Arg
100 105 110

Asp Val Leu Arg Val Gly Ser Gly Gly Phe Trp Pro Arg Arg Ser Arg
115 120 125

Leu Trp Gly Gly Val Asp His Ala Pro Ala Gly Phe Asn Pro Thr Val

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Thr Val Phe His Val Tyr Asp Ile Leu Glu Asn Val Glu His Ala Tyr
145                 150                 155                 160

Gly Met Arg Ala Ala Gln Phe His Ala Arg Phe Met Asp Ala Ile Thr
                165                 170                 175

Pro Thr Gly Thr Val Ile Thr Leu Leu Gly Leu Thr Pro Glu Gly His
            180                 185                 190

Arg Val Ala Val His Val Tyr Gly Thr Arg Gln Tyr Phe Tyr Met Asn
        195                 200                 205

Lys Glu Glu Val Asp Arg His Leu Gln Cys Arg Ala Pro Arg Asp Leu
    210                 215                 220

Cys Glu Arg Met Ala Ala Ala Leu Arg Glu Ser Pro Gly Ala Ser Phe
225                 230                 235                 240

Arg Gly Ile Ser Ala Asp His Phe Glu Ala Glu Val Val Glu Arg Thr
                245                 250                 255

Asp Val Tyr Tyr Tyr Glu Thr Arg Pro Ala Leu Phe Tyr Arg Val Tyr
            260                 265                 270

Val Arg Ser Gly Arg Val Leu Ser Tyr Leu Cys Asp Asn Phe Cys Pro
        275                 280                 285

Ala Ile Lys Lys Tyr Glu Gly Gly Val Asp Ala Thr Thr Arg Phe Ile
    290                 295                 300

Leu Asp Asn Pro Gly Phe Val Thr Phe Gly Trp Tyr Arg Leu Lys Pro
305                 310                 315                 320

Gly Arg Asn Asn Thr Leu Ala Gln Pro Arg Ala Pro Met Ala Phe Gly
                325                 330                 335

Thr Ser Ser Asp Val Glu Phe Asn Cys Thr Ala Asp Asn Leu Ala Ile
            340                 345                 350

Glu Gly Gly Met Ser Asp Leu Pro Ala Tyr Lys Leu Met Cys Phe Asp
        355                 360                 365

Ile Glu Cys Lys Ala Gly Gly Glu Asp Glu Leu Ala Phe Pro Val Ala
    370                 375                 380

Gly His Pro Glu Asp Leu Val Ile Gln Ile Ser Cys Leu Leu Tyr Asp
385                 390                 395                 400

Leu Ser Thr Thr Ala Leu Glu His Val Leu Leu Phe Ser Leu Gly Ser
                405                 410                 415

Cys Asp Leu Pro Glu Ser His Leu Asn Glu Leu Ala Ala Arg Gly Leu
            420                 425                 430

Pro Thr Pro Val Val Leu Glu Phe Asp Ser Glu Phe Glu Met Leu Leu
        435                 440                 445

Ala Phe Met Thr Leu Val Lys Gln Tyr Gly Pro Glu Phe Val Thr Gly
    450                 455                 460
```

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Tyr Asn Ile Ile Asn Phe Asp Trp Pro Phe Leu Leu Ala Lys Leu Thr
465                 470                 475                 480

Asp Ile Tyr Lys Val Pro Leu Asp Gly Tyr Gly Arg Met Asn Gly Arg
                485                 490                 495

Gly Val Phe Arg Val Trp Asp Ile Gly Gln Ser His Phe Gln Lys Arg
            500                 505                 510

Ser Lys Ile Lys Val Asn Gly Met Val Asn Ile Asp Met Tyr Gly Ile
        515                 520                 525

Ile Thr Asp Lys Ile Lys Leu Ser Ser Tyr Lys Leu Asn Ala Val Ala
    530                 535                 540

Glu Ala Val Leu Lys Asp Lys Lys Lys Asp Leu Ser Tyr Arg Asp Ile
545                 550                 555                 560

Pro Ala Tyr Tyr Ala Ala Gly Pro Ala Gln Arg Gly Val Ile Gly Glu
                565                 570                 575

Tyr Cys Ile Gln Asp Ser Leu Leu Val Gly Gln Leu Phe Phe Lys Phe
            580                 585                 590

Leu Pro His Leu Glu Leu Ser Ala Val Ala Arg Leu Ala Gly Ile Asn
        595                 600                 605

Ile Thr Arg Thr Ile Tyr Asp Gly Gln Gln Ile Arg Val Phe Thr Cys
    610                 615                 620

Leu Leu Arg Leu Ala Asp Gln Lys Gly Phe Ile Leu Pro Asp Thr Gln
625                 630                 635                 640

Gly Arg Phe Arg Gly Ala Gly Gly Glu Ala Pro Lys Arg Pro Ala Ala
                645                 650                 655

Ala Arg Glu Asp Glu Glu Arg Pro Glu Glu Glu Gly Glu Asp Glu Asp
            660                 665                 670

Glu Arg Glu Glu Gly Gly Gly Glu Arg Glu Pro Glu Gly Ala Arg Glu
        675                 680                 685

Thr Ala Gly Arg His Val Gly Tyr Gln Gly Ala Arg Val Leu Asp Pro
    690                 695                 700

Thr Ser Gly Phe His Val Asn Pro Val Val Val Phe Asp Phe Ala Ser
705                 710                 715                 720

Leu Tyr Pro Ser Ile Ile Gln Ala His Asn Leu Cys Phe Ser Thr Leu
                725                 730                 735

Ser Leu Arg Ala Asp Ala Val Ala His Leu Glu Ala Gly Lys Asp Tyr
            740                 745                 750

Leu Glu Ile Glu Val Gly Gly Arg Arg Leu Phe Phe Val Lys Ala His
        755                 760                 765

Val Arg Glu Ser Leu Leu Ser Ile Leu Leu Arg Asp Trp Leu Ala Met
    770                 775                 780

Arg Lys Gln Ile Arg Ser Arg Ile Pro Gln Ser Ser Pro Glu Glu Ala
785                 790                 795                 800
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Val Leu Leu Asp Lys Gln Gln Ala Ala Ile Lys Val Val Cys Asn Ser
                805                 810                 815

Val Tyr Gly Phe Thr Gly Ala Gln His Gly Leu Leu Pro Cys Leu His
            820                 825                 830

Val Ala Ala Thr Val Thr Thr Ile Gly Arg Glu Met Leu Leu Ala Thr
        835                 840                 845

Arg Glu Tyr Val His Ala Arg Trp Ala Ala Phe Glu Gln Leu Leu Ala
    850                 855                 860

Asp Phe Pro Glu Ala Ala Asp Met Arg Ala Pro Gly Pro Tyr Ser Met
865                 870                 875                 880

Arg Ile Ile Tyr Gly Asp Thr Asp Ser Ile Phe Val Leu Cys Arg Gly
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Leu Thr Ala Ala Gly Leu Thr Ala Met Gly Asp Lys Met Ala Ser His
            900                 905                 910

Ile Ser Arg Ala Leu Phe Leu Pro Pro Ile Lys Leu Glu Cys Glu Lys
        915                 920                 925

Thr Phe Thr Lys Leu Leu Leu Ile Ala Lys Lys Lys Tyr Ile Gly Val
    930                 935                 940

Ile Tyr Gly Gly Lys Met Leu Ile Lys Gly Val Asp Leu Val Arg Lys
945                 950                 955                 960

Asn Asn Cys Ala Phe Ile Asn Arg Thr Ser Arg Ala Leu Val Asp Leu
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Leu Phe Tyr Asp Asp Thr Val Ser Gly Ala Ala Ala Ala Leu Ala Glu
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Arg Pro Ala Glu Glu Trp Leu Ala  Arg Pro Leu Pro Glu  Gly Leu Gln
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Ala Phe  Gly Ala Val Leu Val  Asp Ala His Arg Arg  Ile Thr Asp
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Pro Glu  Arg Asp Ile Gln Asp  Phe Val Leu Thr Ala  Glu Leu Ser
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Arg His  Pro Arg Ala Tyr Thr  Asn Lys Arg Leu Ala  His Leu Thr
    1040                1045                1050

Val Tyr  Tyr Lys Leu Met Ala  Arg Arg Ala Gln Val  Pro Ser Ile
    1055                1060                1065

Lys Asp  Arg Ile Pro Tyr Val  Ile Val Ala Gln Thr  Arg Glu Val
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Glu Glu  Thr Val Ala Arg Leu  Ala Ala Leu Arg Glu  Leu Asp Ala
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Ala Ala  Pro Gly Asp Glu Pro  Ala Pro Pro Ala Ala  Leu Pro Ser
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Pro Ala  Lys Arg Pro Arg Glu  Thr Pro Ser His Ala  Asp Pro Pro
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Gly Gly Ala Ser Lys Pro Arg Lys Leu Leu Val Ser Glu Leu Ala
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Glu Asp Pro Ala Tyr Ala Ile Ala His Gly Val Ala Leu Asn Thr
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Asp Tyr Tyr Phe Ser His Leu Leu Gly Ala Ala Cys Val Thr Phe
1160 1165 1170

Lys Ala Leu Phe Gly Asn Asn Ala Lys Ile Thr Glu Ser Leu Leu
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Lys Arg Phe Ile Pro Glu Val Trp His Pro Pro Asp Asp Val Ala
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Ala Arg Leu Arg Ala Ala Gly Phe Gly Ala Val Gly Ala Gly Ala
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Thr Ala Glu Glu Thr Arg Arg Met Leu His Arg Ala Phe Asp Thr
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Leu Ala
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Gly Arg Gly Pro Pro Pro Cys Leu Arg Gln Asn Phe Tyr Asn Pro Tyr
35 40 45

Leu Ala Pro Val Gly Thr Gln Gln Lys Pro Thr Gly Pro Thr Gln Arg
50 55 60

His Thr Tyr Tyr Ser Glu Cys Asp Glu Phe Arg Phe Ile Ala Pro Arg
65 70 75 80

Val Leu Asp Glu Asp Ala Pro Pro Glu Lys Arg Ala Gly Val His Asp
85 90 95

Gly His Leu Lys Arg Ala Pro Lys Val Tyr Cys Gly Gly Asp Glu Arg
100 105 110

Asp Val Leu Arg Val Gly Ser Gly Gly Phe Trp Pro Arg Arg Ser Arg

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        115                 120                 125

Leu Trp Gly Gly Val Asp His Ala Pro Ala Gly Phe Asn Pro Thr Val
    130                 135                 140

Thr Val Phe His Val Tyr Asp Ile Leu Glu Asn Val Glu His Ala Tyr
145                 150                 155                 160

Gly Met Arg Ala Ala Gln Phe His Ala Arg Phe Met Asp Ala Ile Thr
                165                 170                 175

Pro Thr Gly Thr Val Ile Thr Leu Leu Gly Leu Thr Pro Glu Gly His
            180                 185                 190

Arg Val Ala Val His Val Tyr Gly Thr Arg Gln Tyr Phe Tyr Met Asn
        195                 200                 205

Lys Glu Glu Val Asp Arg His Leu Gln Cys Arg Ala Pro Arg Asp Leu
    210                 215                 220

Cys Glu Arg Met Ala Ala Ala Leu Arg Glu Ser Pro Gly Ala Ser Phe
225                 230                 235                 240

Arg Gly Ile Ser Ala Asp His Phe Glu Ala Glu Val Val Glu Arg Thr
                245                 250                 255

Asp Val Tyr Tyr Tyr Glu Thr Arg Pro Ala Leu Phe Tyr Arg Val Tyr
            260                 265                 270

Val Arg Ser Gly Arg Val Leu Ser Tyr Leu Cys Asp Asn Phe Cys Pro
        275                 280                 285

Ala Ile Lys Lys Tyr Glu Gly Gly Val Asp Ala Thr Thr Arg Phe Ile
    290                 295                 300

Leu Asp Asn Pro Gly Phe Val Thr Phe Gly Trp Tyr Arg Leu Lys Pro
305                 310                 315                 320

Gly Arg Asn Asn Thr Leu Ala Gln Pro Arg Ala Pro Met Ala Phe Gly
                325                 330                 335

Thr Ser Ser Asp Val Glu Phe Asn Cys Thr Ala Asp Asn Leu Ala Ile
            340                 345                 350

Glu Gly Gly Met Ser Asp Leu Pro Ala Tyr Lys Leu Met Cys Phe Asp
        355                 360                 365

Ile Glu Cys Lys Ala Gly Gly Glu Asp Glu Leu Ala Phe Pro Val Ala
    370                 375                 380

Gly His Pro Glu Asp Leu Val Ile Gln Ile Ser Cys Leu Leu Tyr Asp
385                 390                 395                 400

Leu Ser Thr Thr Ala Leu Glu His Val Leu Leu Phe Ser Leu Gly Ser
                405                 410                 415

Cys Asp Leu Pro Glu Ser His Leu Asn Glu Leu Ala Ala Arg Gly Leu
            420                 425                 430

Pro Thr Pro Val Val Leu Glu Phe Asp Ser Glu Phe Glu Met Leu Leu
        435                 440                 445
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Ala Phe Met Thr Leu Val Lys Gln Tyr Gly Pro Glu Phe Val Thr Gly
    450                 455                 460

Tyr Asn Ile Ile Asn Phe Asp Trp Pro Phe Leu Leu Ala Lys Leu Thr
465                 470                 475                 480

Asp Ile Tyr Lys Val Pro Leu Asp Gly Tyr Gly Arg Met Asn Gly Arg
                485                 490                 495

Gly Val Phe Arg Val Trp Asp Ile Gly Gln Ser His Phe Gln Lys Arg
            500                 505                 510

Ser Lys Ile Lys Val Asn Gly Met Val Asn Ile Asp Met Tyr Gly Ile
        515                 520                 525

Ile Thr Asp Lys Ile Lys Leu Ser Ser Tyr Lys Leu Asn Ala Val Ala
    530                 535                 540

Glu Ala Val Leu Lys Asp Lys Lys Lys Asp Leu Ser Tyr Arg Asp Ile
545                 550                 555                 560

Pro Ala Tyr Tyr Ala Ala Gly Pro Ala Gln Arg Gly Val Ile Gly Glu
                565                 570                 575

Tyr Cys Ile Gln Asp Ser Leu Leu Val Gly Gln Leu Phe Phe Lys Phe
            580                 585                 590

Leu Pro His Leu Glu Leu Ser Ala Val Ala Arg Leu Ala Gly Ile Asn
        595                 600                 605

Ile Thr Arg Thr Ile Tyr Asp Gly Gln Gln Ile Arg Val Phe Thr Cys
    610                 615                 620

Leu Leu Arg Leu Ala Asp Gln Lys Gly Phe Ile Leu Pro Asp Thr Gln
625                 630                 635                 640

Gly Arg Phe Arg Gly Gly Gly Gly Glu Ala Pro Lys Arg Pro Ala Ala
                645                 650                 655

Ala Arg Glu Asp Glu Glu Arg Pro Glu Glu Glu Gly Glu Asp Glu Asp
            660                 665                 670

Glu Arg Glu Glu Gly Gly Gly Glu Arg Glu Pro Glu Gly Ala Arg Glu
        675                 680                 685

Thr Ala Gly Arg His Val Gly Tyr Gln Gly Ala Arg Val Leu Asp Pro
    690                 695                 700

Thr Ser Gly Phe His Val Asn Pro Val Val Val Phe Asp Phe Ala Ser
705                 710                 715                 720

Leu Tyr Pro Ser Ile Ile Gln Ala His Asn Leu Cys Phe Ser Thr Leu
                725                 730                 735

Ser Leu Arg Ala Asp Ala Val Ala His Leu Glu Ala Gly Lys Asp Tyr
            740                 745                 750

Leu Glu Ile Glu Val Gly Gly Arg Arg Leu Phe Phe Val Lys Ala His
        755                 760                 765

Val Arg Glu Ser Leu Leu Ser Ile Leu Leu Arg Asp Trp Leu Ala Met
    770                 775                 780
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Arg Lys Gln Ile Arg Ser Arg Ile Pro Gln Ser Ser Pro Glu Glu Ala
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Val Leu Leu Asp Lys Gln Gln Ala Ala Ile Lys Val Val Cys Asn Ser
                805                 810                 815

Val Tyr Gly Phe Thr Gly Ala Gln His Gly Leu Leu Pro Cys Leu His
            820                 825                 830

Val Ala Ala Thr Val Thr Thr Ile Gly Arg Glu Met Leu Leu Ala Thr
        835                 840                 845

Arg Glu Tyr Val His Ala Arg Trp Ala Ala Phe Glu Gln Leu Leu Ala
    850                 855                 860

Asp Phe Pro Glu Ala Ala Asp Met Arg Ala Pro Gly Pro Tyr Ser Met
865                 870                 875                 880

Arg Ile Ile Tyr Gly Asp Thr Asp Ser Ile Phe Val Leu Cys Arg Gly
                885                 890                 895

Leu Thr Ala Ala Gly Leu Thr Ala Val Gly Asp Lys Met Ala Ser His
            900                 905                 910

Ile Ser Arg Ala Leu Phe Leu Ser Pro Ile Lys Leu Glu Cys Glu Lys
        915                 920                 925

Thr Phe Thr Lys Leu Leu Leu Ile Ala Lys Lys Lys Tyr Ile Gly Val
    930                 935                 940

Ile Tyr Gly Gly Lys Met Leu Ile Lys Gly Val Asp Leu Val Arg Lys
945                 950                 955                 960

Asn Asn Cys Ala Phe Ile Asn Arg Thr Ser Arg Ala Leu Val Asp Leu
                965                 970                 975

Leu Phe Tyr Asp Asp Thr Val Ser Gly Ala Ala Ala Ala Leu Ala Glu
            980                 985                 990

Arg Pro Ala Glu Glu Trp Leu Ala  Arg Pro Leu Pro Glu  Gly Leu Gln
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Ala Phe  Gly Ala Val Leu Val  Asp Ala His Arg Arg  Ile Thr Asp
    1010                1015                1020

Pro Glu  Arg Asp Ile Gln Asp  Phe Val Leu Thr Ala  Glu Leu Ser
    1025                1030                1035

Arg His  Pro Arg Ala Tyr Thr  Asn Lys Arg Leu Ala  His Leu Thr
    1040                1045                1050

Val Tyr  Tyr Lys Leu Met Ala  Arg Arg Ala Gln Val  Pro Ser Ile
    1055                1060                1065

Lys Asp  Arg Ile Pro Tyr Val  Ile Val Ala Gln Thr  Arg Glu Val
    1070                1075                1080

Glu Glu  Thr Val Ala Arg Leu  Ala Ala Leu Arg Glu  Leu Asp Ala
    1085                1090                1095

Ala Ala  Pro Gly Asp Glu Pro  Ala Pro Pro Ala Ala  Leu Pro Ser
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1100 1105 1110

Pro Ala Lys Arg Pro Arg Glu Thr Pro Leu His Ala Asp Pro Pro
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Gly Gly Ala Ser Lys Pro Arg Lys Leu Leu Val Ser Glu Leu Ala
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Glu Asp Pro Ala Tyr Ala Ile Ala His Gly Val Ala Leu Asn Thr
1145 1150 1155

Asp Tyr Tyr Phe Ser His Leu Leu Gly Ala Ala Cys Val Thr Phe
1160 1165 1170

Lys Ala Leu Phe Gly Asn Asn Ala Lys Ile Thr Glu Ser Leu Leu
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Lys Arg Phe Ile Pro Glu Val Trp His Pro Pro Asp Asp Val Ala
1190 1195 1200

Ala Arg Leu Arg Ala Ala Gly Phe Gly Ala Val Gly Ala Gly Ala
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Thr Ala Glu Glu Thr Arg Arg Met Leu His Arg Ala Phe Asp Thr
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Leu Ala
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<400> 10

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Gly Arg Gly Pro Pro Pro Cys Leu Arg Gln Asn Phe Tyr Asn Pro Tyr
35 40 45

Leu Ala Pro Val Gly Thr Gln Gln Lys Pro Thr Gly Pro Thr Gln Arg
50 55 60

His Thr Tyr Tyr Ser Glu Cys Asp Glu Phe Arg Phe Ile Ala Pro Arg
65 70 75 80

Val Leu Asp Glu Asp Ala Pro Pro Glu Lys Arg Ala Gly Val His Asp
85 90 95

Gly His Leu Lys Arg Ala Pro Lys Val Tyr Cys Gly Gly Asp Glu Arg

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Asp Val Leu Arg Val Gly Ser Gly Gly Phe Trp Pro Arg Arg Ser Arg
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Leu Trp Gly Gly Val Asp His Ala Pro Ala Gly Phe Asn Pro Thr Val
    130                 135                 140

Thr Val Phe His Val Tyr Asp Ile Leu Glu Asn Val Glu His Ala Tyr
145                 150                 155                 160

Gly Met Arg Ala Ala Gln Phe His Ala Arg Phe Met Asp Ala Ile Thr
                165                 170                 175

Pro Thr Gly Thr Val Ile Thr Leu Leu Gly Leu Thr Pro Glu Gly His
            180                 185                 190

Arg Val Ala Val His Val Tyr Gly Thr Arg Gln Tyr Phe Tyr Met Asn
        195                 200                 205

Lys Glu Glu Val Asp Arg His Leu Gln Cys Arg Ala Pro Arg Asp Leu
    210                 215                 220

Cys Glu Arg Met Ala Ala Ala Leu Arg Glu Ser Pro Gly Ala Ser Phe
225                 230                 235                 240

Arg Gly Ile Ser Ala Asp His Phe Glu Ala Glu Val Val Glu Arg Thr
                245                 250                 255

Asp Val Tyr Tyr Tyr Glu Thr Arg Pro Ala Leu Phe Tyr Arg Val Tyr
            260                 265                 270

Val Arg Ser Gly Arg Val Leu Ser Tyr Leu Cys Asp Asn Phe Cys Pro
        275                 280                 285

Ala Ile Lys Lys Tyr Glu Gly Gly Val Asp Ala Thr Thr Arg Phe Ile
    290                 295                 300

Leu Asp Asn Pro Gly Phe Val Thr Phe Gly Trp Tyr Arg Leu Lys Pro
305                 310                 315                 320

Gly Arg Asn Asn Thr Leu Ala Gln Pro Arg Ala Pro Met Ala Phe Gly
                325                 330                 335

Thr Ser Ser Asp Val Glu Phe Asn Cys Thr Ala Asp Asn Leu Ala Ile
            340                 345                 350

Glu Gly Gly Met Ser Asp Leu Pro Ala Tyr Lys Leu Met Cys Phe Asp
        355                 360                 365

Ile Glu Cys Lys Ala Gly Gly Glu Asp Glu Leu Ala Phe Pro Val Ala
    370                 375                 380

Gly His Pro Glu Asp Leu Val Ile Gln Ile Ser Cys Leu Leu Tyr Asp
385                 390                 395                 400

Leu Ser Thr Thr Ala Leu Glu His Val Leu Leu Phe Ser Leu Gly Ser
                405                 410                 415

Cys Asp Leu Pro Glu Ser His Leu Asn Glu Leu Ala Ala Arg Gly Leu
            420                 425                 430
```

```
Pro Thr Pro Val Val Leu Glu Phe Asp Ser Glu Phe Glu Met Leu Leu
        435                 440                 445

Ala Phe Met Thr Leu Val Lys Gln Tyr Gly Pro Glu Phe Val Thr Gly
    450                 455                 460

Tyr Asn Ile Ile Asn Phe Asp Trp Pro Phe Leu Leu Ala Lys Leu Thr
465                 470                 475                 480

Asp Ile Tyr Lys Val Pro Leu Asp Gly Tyr Gly Arg Met Asn Gly Arg
                485                 490                 495

Gly Val Phe Arg Val Trp Asp Ile Gly Gln Ser His Phe Gln Lys Arg
            500                 505                 510

Ser Lys Ile Lys Val Asn Gly Met Val Asn Ile Asp Met Tyr Gly Ile
        515                 520                 525

Ile Thr Asp Lys Ile Lys Leu Ser Ser Tyr Lys Leu Asn Ala Val Ala
    530                 535                 540

Glu Ala Val Leu Lys Asp Lys Lys Lys Asp Leu Ser Tyr Arg Asp Ile
545                 550                 555                 560

Pro Thr Tyr Tyr Ala Ala Gly Pro Ala Gln Arg Gly Val Ile Gly Glu
                565                 570                 575

Tyr Cys Ile Gln Asp Ser Leu Leu Val Gly Gln Leu Phe Phe Lys Phe
            580                 585                 590

Leu Pro His Leu Glu Leu Ser Ala Val Ala Arg Leu Ala Gly Ile Asn
        595                 600                 605

Ile Thr Arg Thr Ile Tyr Asp Gly Gln Gln Ile Arg Val Phe Thr Cys
    610                 615                 620

Leu Leu Arg Leu Ala Asp Gln Lys Gly Phe Ile Leu Pro Asp Thr Gln
625                 630                 635                 640

Gly Arg Phe Arg Gly Ala Gly Gly Glu Ala Pro Lys Arg Pro Ala Ala
                645                 650                 655

Ala Arg Glu Asp Glu Glu Arg Pro Glu Glu Glu Gly Glu Asp Glu Asn
            660                 665                 670

Glu Arg Glu Glu Gly Gly Gly Glu Arg Glu Pro Glu Gly Ala Arg Glu
        675                 680                 685

Thr Ala Gly Arg His Val Gly Tyr Gln Gly Ala Arg Val Leu Asp Pro
    690                 695                 700

Thr Ser Gly Phe His Val Asn Pro Val Val Val Phe Asp Phe Ala Ser
705                 710                 715                 720

Leu Tyr Pro Ser Ile Ile Gln Ala His Asn Leu Cys Phe Ser Thr Leu
                725                 730                 735

Ser Leu Arg Ala Asp Ala Val Ala His Leu Glu Ala Gly Lys Asp Tyr
            740                 745                 750

Leu Glu Ile Glu Val Gly Gly Arg Arg Leu Phe Phe Val Lys Ala His
        755                 760                 765
```

```
Val Arg Glu Ser Leu Leu Ser Ile Leu Leu Arg Asp Trp Leu Ala Met
    770                 775                 780

Arg Lys Gln Ile Arg Ser Arg Ile Pro Gln Ser Ser Pro Glu Glu Ala
785                 790                 795                 800

Val Leu Leu Asp Lys Gln Gln Ala Ala Ile Lys Val Val Cys Asn Ser
                805                 810                 815

Val Tyr Gly Phe Thr Gly Ala Gln His Gly Leu Leu Pro Cys Leu His
            820                 825                 830

Val Ala Ala Thr Val Thr Thr Ile Gly Arg Glu Met Leu Leu Ala Thr
        835                 840                 845

Arg Glu Tyr Val His Ala Arg Trp Ala Ala Phe Glu Gln Leu Leu Ala
    850                 855                 860

Asp Phe Pro Glu Ala Ala Asp Met Arg Ala Pro Gly Pro Tyr Ser Met
865                 870                 875                 880

Arg Ile Ile Tyr Gly Asp Thr Asp Ser Ile Phe Val Leu Cys Arg Gly
                885                 890                 895

Leu Thr Ala Ala Gly Leu Thr Ala Val Gly Asp Lys Met Ala Ser His
            900                 905                 910

Ile Ser Arg Ala Leu Phe Leu Pro Pro Ile Lys Leu Glu Cys Glu Lys
        915                 920                 925

Thr Phe Thr Lys Leu Leu Leu Ile Ala Lys Lys Lys Tyr Ile Gly Val
    930                 935                 940

Ile Tyr Gly Gly Lys Met Leu Ile Lys Gly Val Asp Leu Val Arg Lys
945                 950                 955                 960

Asn Asn Cys Ala Phe Ile Asn Arg Thr Ser Arg Ala Leu Val Asp Leu
                965                 970                 975

Leu Phe Tyr Asp Asp Thr Val Ser Gly Ala Ala Ala Ala Leu Ala Glu
            980                 985                 990

Arg Pro Ala Glu Glu Trp Leu Ala  Arg Pro Leu Pro Glu  Gly Leu Gln
        995                 1000                1005

Ala Phe  Gly Ala Val Leu Val  Asp Ala His Arg Arg  Ile Thr Asp
    1010                1015                1020

Pro Glu  Arg Asp Ile Gln Asp  Phe Val Leu Thr Ala  Glu Leu Ser
    1025                1030                1035

Arg His  Pro Arg Ala Tyr Thr  Asn Lys Arg Leu Ala  His Leu Thr
    1040                1045                1050

Val Tyr  Tyr Lys Leu Met Ala  Arg Arg Ala Gln Val  Pro Ser Ile
    1055                1060                1065

Lys Asp  Arg Ile Pro Tyr Val  Ile Val Ala Gln Thr  Arg Glu Val
    1070                1075                1080

Glu Glu  Thr Val Ala Arg Leu  Ala Ala Leu Arg Glu  Leu Asp Ala
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1085 1090 1095

Ala Ala Pro Gly Asp Glu Pro Ala Pro Pro Ala Ala Leu Pro Ser
1100 1105 1110

Pro Ala Lys Arg Pro Arg Glu Thr Pro Ser Pro Ala Asp Pro Pro
1115 1120 1125

Gly Gly Ala Ser Lys Pro Arg Lys Leu Leu Val Ser Glu Leu Ala
1130 1135 1140

Glu Asp Pro Ala Tyr Ala Ile Ala His Gly Val Ala Leu Asn Thr
1145 1150 1155

Asp Tyr Tyr Phe Ser His Leu Leu Gly Ala Ala Cys Val Thr Phe
1160 1165 1170

Lys Ala Leu Phe Gly Asn Asn Ala Lys Ile Thr Glu Ser Leu Leu
1175 1180 1185

Lys Arg Phe Ile Pro Glu Val Trp His Pro Pro Asp Asp Val Ala
1190 1195 1200

Ala Arg Leu Arg Thr Ala Gly Phe Gly Ala Val Gly Ala Gly Ala
1205 1210 1215

Thr Ala Glu Glu Thr Arg Arg Met Leu His Arg Ala Phe Asp Thr
1220 1225 1230

Leu Ala
1235

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cgtcagcgtt cgcagcccgg ctccgcgcag ggctcgggca agcggccgcc acagaaacag 120

tttttgcaga tcgtgccgcg aggtgtcatg ttcgacggtc agacggggtt gatcaagcat 180

aagacgggac ggctgcctct catgttctat cgagagatta aacatttgtt gagtcatgac 240

atggtttggc cgtgtccttg gcgcgagacc ctggtgggtc gcgtggtggg acctattcgt 300

tttcacacct acgatcagac ggacgccgtg ctcttcttcg actcgcccga aaacgtgtcg 360

ccgcgctatc gtcagcatct ggtgccttcg gggaacgtgt tgcgtttctt cggggccaca 420

gaacacggct acagtatctg cgtcaacgtt ttcgggcagc gcagctactt ttactgtgag 480

tacagcgaca ccgataggct gcgtgaggtc attgccagcg tgggcgaact agtgcccgaa 540

ccgcggacgc catacgccgt gtctgtcacg ccggccacca agacctccat ctatgggtac 600

gggacgcgac ccgtgcccga tttgcagtgt gtgtctatca gcaactggac catggccaga 660

aaaatcggcg agtatctgct ggagcagggt tttcccgtgt acgaggtccg tgtggatccg 720

ctgacgcgtt tggtcatcga tcggcggatc accacgttcg gctggtgctc cgtgaatcgt 780

tacgactggc ggcagcaggg tcgcgcgtcg acttgtgata tcgaggtaga ctgcgatgtc 840

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gatatcgagt gcatgagcgg cgagggtggt tttccctgcg ccgagaagtc cgatgacatt 960

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atcccgcgtt gtttcgtggc taatgccgag ggccgcgccc aggtaggccg ttactgtctg 1620

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tcgccgccct tgcaatctgc gccgtccagt caggacggcg tttcacccgg ctccggcagt 1980

aacagtagta gcagcgtcgg cgttttcagc gtcggctccg gcagtagtgg cggcgtcggc 2040

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gtgtttgagc ccgaggtggg ttactacaac gaccccgtgg ccgtgttcga ctttgccagc 2160

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tgctgttga 3729

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Met Phe Phe Asn Pro Tyr Leu Ser Gly Gly Val Thr Gly Gly Ala Val
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Ala Gly Gly Arg Arg Gln Arg Ser Gln Pro Gly Ser Ala Gln Gly Ser
20 25 30

Gly Lys Arg Pro Pro Gln Lys Gln Phe Leu Gln Ile Val Pro Arg Gly
35 40 45

Val Met Phe Asp Gly Gln Thr Gly Leu Ile Lys His Lys Thr Gly Arg
50 55 60

Leu Pro Leu Met Phe Tyr Arg Glu Ile Lys His Leu Leu Ser His Asp
65 70 75 80

```
Met Val Trp Pro Cys Pro Trp Arg Glu Thr Leu Val Gly Arg Val Val
                85                  90                  95

Gly Pro Ile Arg Phe His Thr Tyr Asp Gln Thr Asp Ala Val Leu Phe
            100                 105                 110

Phe Asp Ser Pro Glu Asn Val Ser Pro Arg Tyr Arg Gln His Leu Val
        115                 120                 125

Pro Ser Gly Asn Val Leu Arg Phe Phe Gly Ala Thr Glu His Gly Tyr
    130                 135                 140

Ser Ile Cys Val Asn Val Phe Gly Gln Arg Ser Tyr Phe Tyr Cys Glu
145                 150                 155                 160

Tyr Ser Asp Thr Asp Arg Leu Arg Glu Val Ile Ala Ser Val Gly Glu
                165                 170                 175

Leu Val Pro Glu Pro Arg Thr Pro Tyr Ala Val Ser Val Thr Pro Ala
            180                 185                 190

Thr Lys Thr Ser Ile Tyr Gly Tyr Gly Thr Arg Pro Val Pro Asp Leu
        195                 200                 205

Gln Cys Val Ser Ile Ser Asn Trp Thr Met Ala Arg Lys Ile Gly Glu
    210                 215                 220

Tyr Leu Leu Glu Gln Gly Phe Pro Val Tyr Glu Val Arg Val Asp Pro
225                 230                 235                 240

Leu Thr Arg Leu Val Ile Asp Arg Arg Ile Thr Thr Phe Gly Trp Cys
                245                 250                 255

Ser Val Asn Arg Tyr Asp Trp Arg Gln Gln Gly Arg Ala Ser Thr Cys
            260                 265                 270

Asp Ile Glu Val Asp Cys Asp Val Ser Asp Leu Val Ala Val Pro Asp
        275                 280                 285

Asp Ser Ser Trp Pro Arg Tyr Arg Cys Leu Ser Phe Asp Ile Glu Cys
    290                 295                 300

Met Ser Gly Glu Gly Gly Phe Pro Cys Ala Glu Lys Ser Asp Asp Ile
305                 310                 315                 320

Val Ile Gln Ile Ser Cys Val Cys Tyr Glu Thr Gly Gly Asn Thr Ala
                325                 330                 335

Val Asp Gln Gly Ile Pro Asn Gly Asn Asp Gly Arg Gly Cys Thr Ser
            340                 345                 350

Glu Gly Val Ile Phe Gly His Ser Gly Leu His Leu Phe Thr Ile Gly
        355                 360                 365

Thr Cys Gly Gln Val Gly Pro Asp Val Asp Val Tyr Glu Phe Pro Ser
    370                 375                 380

Glu Tyr Glu Leu Leu Leu Gly Phe Met Leu Phe Phe Gln Arg Tyr Ala
385                 390                 395                 400

Pro Ala Phe Val Thr Gly Tyr Asn Ile Asn Ser Phe Asp Leu Lys Tyr
```

```
                405                 410                 415

Ile Leu Thr Arg Leu Glu Tyr Leu Tyr Lys Val Asp Ser Gln Arg Phe
            420                 425                 430

Cys Lys Leu Pro Thr Ala Gln Gly Gly Arg Phe Phe Leu His Ser Pro
        435                 440                 445

Ala Val Gly Phe Lys Arg Gln Tyr Ala Ala Ala Phe Pro Ser Ala Ser
    450                 455                 460

His Asn Asn Pro Ala Ser Thr Ala Ala Thr Lys Val Tyr Ile Ala Gly
465                 470                 475                 480

Ser Val Val Ile Asp Met Tyr Pro Val Cys Met Ala Lys Thr Asn Ser
                485                 490                 495

Pro Asn Tyr Lys Leu Asn Thr Met Ala Glu Leu Tyr Leu Arg Gln Arg
            500                 505                 510

Lys Asp Asp Leu Ser Tyr Lys Asp Ile Pro Arg Cys Phe Val Ala Asn
        515                 520                 525

Ala Glu Gly Arg Ala Gln Val Gly Arg Tyr Cys Leu Gln Asp Ala Val
    530                 535                 540

Leu Val Arg Asp Leu Phe Asn Thr Ile Asn Phe His Tyr Glu Ala Gly
545                 550                 555                 560

Ala Ile Ala Arg Leu Ala Lys Ile Pro Leu Arg Arg Val Ile Phe Asp
                565                 570                 575

Gly Gln Gln Ile Arg Ile Tyr Thr Ser Leu Leu Asp Glu Cys Ala Cys
            580                 585                 590

Arg Asp Phe Ile Leu Pro Asn His Tyr Ser Lys Gly Thr Thr Val Pro
        595                 600                 605

Glu Thr Asn Ser Val Ala Val Ser Pro Asn Ala Ala Ile Ile Ser Thr
    610                 615                 620

Ala Ala Val Pro Gly Asp Ala Gly Ser Val Ala Ala Met Phe Gln Met
625                 630                 635                 640

Ser Pro Pro Leu Gln Ser Ala Pro Ser Ser Gln Asp Gly Val Ser Pro
                645                 650                 655

Gly Ser Gly Ser Asn Ser Ser Ser Ser Val Gly Val Phe Ser Val Gly
            660                 665                 670

Ser Gly Ser Ser Gly Gly Val Gly Val Ser Asn Asp Asn His Gly Ala
        675                 680                 685

Gly Gly Thr Ala Ala Val Ser Tyr Gln Gly Ala Thr Val Phe Glu Pro
    690                 695                 700

Glu Val Gly Tyr Tyr Asn Asp Pro Val Ala Val Phe Asp Phe Ala Ser
705                 710                 715                 720

Leu Tyr Pro Ser Ile Ile Met Ala His Asn Leu Cys Tyr Ser Thr Leu
                725                 730                 735
```

```
Leu Val Pro Gly Gly Glu Tyr Pro Val Asp Pro Ala Asp Val Tyr Ser
            740                 745                 750

Val Thr Leu Glu Asn Gly Val Thr His Arg Phe Val Arg Ala Ser Val
        755                 760                 765

Arg Val Ser Val Leu Ser Glu Leu Leu Asn Lys Trp Val Ser Gln Arg
    770                 775                 780

Arg Ala Val Arg Glu Cys Met Arg Glu Cys Gln Asp Pro Val Arg Arg
785                 790                 795                 800

Met Leu Leu Asp Lys Glu Gln Met Ala Leu Lys Val Thr Cys Asn Ala
                805                 810                 815

Phe Tyr Gly Phe Thr Gly Ala Leu Asn Gly Met Met Pro Cys Leu Pro
            820                 825                 830

Ile Ala Ala Ser Ile Thr Arg Ile Gly Arg Asp Met Leu Glu Arg Thr
        835                 840                 845

Ala Arg Phe Ile Lys Asp Asn Phe Ser Glu Pro Cys Phe Leu His Asn
    850                 855                 860

Phe Phe Asn Gln Glu Asp Tyr Val Val Gly Thr Arg Glu Gly Asp Ser
865                 870                 875                 880

Glu Glu Ser Ser Ala Leu Pro Glu Gly Leu Glu Thr Ser Ser Gly Gly
                885                 890                 895

Ser Asn Glu Arg Arg Val Glu Ala Arg Val Ile Tyr Gly Asp Thr Asp
            900                 905                 910

Ser Val Phe Val Arg Phe Arg Gly Leu Thr Pro Gln Ala Leu Val Ala
        915                 920                 925

Arg Gly Pro Ser Leu Ala His Tyr Val Thr Ala Cys Leu Phe Val Glu
    930                 935                 940

Pro Val Lys Leu Glu Phe Glu Lys Val Phe Val Ser Leu Met Met Ile
945                 950                 955                 960

Cys Lys Lys Arg Tyr Ile Gly Lys Val Glu Gly Ala Ser Gly Leu Ser
                965                 970                 975

Met Lys Gly Val Asp Leu Val Arg Lys Thr Ala Cys Glu Phe Val Lys
            980                 985                 990

Gly Val Thr Arg Asp Val Leu Ser  Leu Leu Phe Glu Asp  Arg Glu Val
        995                 1000                1005

Ser Glu  Ala Ala Val Arg Leu  Ser Arg Leu Ser Leu  Asp Glu Val
    1010                1015                1020

Lys Lys  Tyr Gly Val Pro Arg  Gly Phe Trp Arg Ile  Leu Arg Arg
    1025                1030                1035

Leu Val  Gln Ala Arg Asp Asp  Leu Tyr Leu His Arg  Val Arg Val
    1040                1045                1050

Glu Asp  Leu Val Leu Ser Ser  Val Leu Ser Lys Asp  Ile Ser Leu
    1055                1060                1065
```

Tyr Arg Gln Ser Asn Leu Pro His Ile Ala Val Ile Lys Arg Leu
1070 1075 1080

Ala Ala Arg Ser Glu Glu Leu Pro Ser Val Gly Asp Arg Val Phe
1085 1090 1095

Tyr Val Leu Thr Ala Pro Gly Val Arg Thr Ala Pro Gln Gly Ser
1100 1105 1110

Ser Asp Asn Gly Asp Ser Val Thr Ala Gly Val Val Ser Arg Ser
1115 1120 1125

Asp Ala Ile Asp Gly Thr Asp Asp Asp Ala Asp Gly Gly Gly Val
1130 1135 1140

Glu Glu Ser Asn Arg Arg Gly Gly Glu Pro Ala Lys Lys Arg Ala
1145 1150 1155

Arg Lys Pro Pro Ser Ala Val Cys Asn Tyr Glu Val Ala Glu Asp
1160 1165 1170

Pro Ser Tyr Val Arg Glu His Gly Val Pro Ile His Ala Asp Lys
1175 1180 1185

Tyr Phe Glu Gln Val Leu Lys Ala Val Thr Asn Val Leu Ser Pro
1190 1195 1200

Val Phe Pro Gly Gly Glu Thr Ala Arg Lys Asp Lys Phe Leu His
1205 1210 1215

Met Val Leu Pro Arg Arg Leu His Leu Glu Pro Ala Phe Leu Pro
1220 1225 1230

Tyr Ser Val Lys Ala His Glu Cys Cys
1235 1240

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Met Phe Phe Asn Pro Tyr Leu Ser Gly Gly Val Thr Gly Gly Ala Val
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Ala Gly Gly Arg Arg Gln Arg Ser Gln Pro Gly Ser Ala Gln Gly Ser
20 25 30

Gly Lys Arg Pro Pro Gln Lys Gln Phe Leu Gln Ile Val Pro Arg Gly
35 40 45

Val Met Phe Asp Gly Gln Thr Gly Leu Ile Lys His Lys Thr Gly Arg
50 55 60

Leu Pro Leu Met Phe Tyr Arg Glu Ile Lys His Leu Leu Ser His Asp
65 70 75 80

Met Val Trp Pro Cys Pro Trp Arg Glu Thr Leu Val Gly Arg Val Val
85 90 95

```
Gly Pro Ile Arg Phe His Thr Tyr Asp Gln Thr Asp Ala Val Leu Phe
            100                 105                 110

Phe Asp Ser Pro Glu Asn Val Ser Pro Arg Tyr Arg Gln His Leu Val
        115                 120                 125

Pro Ser Gly Asn Val Leu Arg Phe Phe Gly Ala Thr Glu His Gly Tyr
    130                 135                 140

Ser Ile Cys Val Asn Val Phe Gly Gln Arg Ser Tyr Phe Tyr Cys Glu
145                 150                 155                 160

Tyr Ser Asp Thr Asp Arg Leu Arg Glu Val Ile Ala Ser Val Gly Glu
                165                 170                 175

Leu Val Pro Glu Pro Arg Thr Pro Tyr Ala Val Ser Val Thr Pro Ala
            180                 185                 190

Thr Lys Thr Ser Ile Tyr Gly Tyr Gly Thr Arg Pro Val Pro Asp Leu
        195                 200                 205

Gln Cys Val Ser Ile Ser Asn Trp Thr Met Ala Arg Lys Ile Gly Glu
    210                 215                 220

Tyr Leu Leu Glu Gln Gly Phe Pro Val Tyr Glu Val Arg Val Asp Pro
225                 230                 235                 240

Leu Thr Arg Leu Val Ile Asp Arg Arg Ile Thr Thr Phe Gly Trp Cys
                245                 250                 255

Ser Val Asn Arg Tyr Asp Trp Arg Gln Gln Gly Arg Ala Ser Thr Cys
            260                 265                 270

Asp Ile Glu Val Asp Cys Asp Val Ser Asp Leu Val Ala Val Pro Asp
        275                 280                 285

Asp Ser Ser Trp Pro Arg Tyr Arg Cys Leu Ser Phe Asp Ile Glu Cys
    290                 295                 300

Met Ser Gly Glu Gly Gly Phe Pro Cys Ala Glu Lys Ser Asp Asp Ile
305                 310                 315                 320

Val Ile Gln Ile Ser Cys Val Cys Tyr Glu Thr Gly Gly Asn Thr Ala
                325                 330                 335

Val Asp Gln Gly Ile Pro Asn Gly Asn Asp Gly Arg Gly Cys Thr Ser
            340                 345                 350

Glu Gly Val Ile Phe Gly His Ser Gly Leu His Leu Phe Thr Ile Gly
        355                 360                 365

Thr Cys Gly Gln Val Gly Pro Asp Val Asp Val Tyr Glu Phe Pro Ser
    370                 375                 380

Glu Tyr Glu Leu Leu Leu Gly Phe Met Leu Phe Phe Gln Arg Tyr Ala
385                 390                 395                 400

Pro Ala Phe Val Thr Gly Tyr Asn Ile Asn Ser Phe Asp Leu Lys Tyr
                405                 410                 415

Ile Leu Thr Arg Leu Glu Tyr Leu Tyr Lys Val Asp Ser Gln Arg Phe
            420                 425                 430
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Cys Lys Leu Pro Thr Ala Gln Gly Gly Arg Phe Phe Leu His Ser Pro
        435                 440                 445

Ala Val Gly Phe Lys Arg Gln Tyr Ala Ala Ala Phe Pro Ser Ala Ser
    450                 455                 460

His Asn Asn Pro Ala Ser Thr Ala Ala Thr Lys Val Tyr Ile Ala Gly
465                 470                 475                 480

Ser Val Val Ile Asp Met Tyr Pro Val Cys Met Ala Lys Thr Asn Ser
                485                 490                 495

Pro Asn Tyr Lys Leu Asn Thr Met Ala Glu Leu Tyr Leu Arg Gln Arg
            500                 505                 510

Lys Asp Asp Leu Ser Tyr Lys Asp Ile Pro Arg Cys Phe Val Ala Asn
        515                 520                 525

Ala Glu Gly Arg Ala Gln Val Gly Arg Tyr Cys Leu Gln Asp Ala Val
    530                 535                 540

Leu Val Arg Asp Leu Phe Asn Thr Ile Asn Phe His Tyr Glu Ala Gly
545                 550                 555                 560

Ala Ile Ala Arg Leu Ala Lys Ile Pro Leu Arg Arg Val Ile Phe Asp
                565                 570                 575

Gly Gln Gln Ile Arg Ile Tyr Thr Ser Leu Leu Asp Glu Cys Ala Cys
            580                 585                 590

Arg Asp Phe Ile Leu Pro Asn His Tyr Ser Lys Gly Thr Thr Val Pro
        595                 600                 605

Glu Thr Asn Ser Val Ala Val Ser Pro Asn Ala Ala Ile Ile Ser Thr
    610                 615                 620

Ala Ala Val Pro Gly Asp Ala Gly Ser Val Ala Ala Met Phe Gln Met
625                 630                 635                 640

Ser Pro Pro Leu Gln Ser Ala Pro Ser Ser Gln Asp Gly Val Ser Pro
                645                 650                 655

Gly Ser Gly Ser Asn Ser Ser Ser Ser Val Gly Val Phe Ser Val Gly
            660                 665                 670

Ser Gly Ser Ser Gly Gly Val Gly Val Ser Asn Asp Asn His Gly Ala
        675                 680                 685

Gly Gly Thr Ala Ala Val Ser Tyr Gln Gly Ala Thr Val Phe Glu Pro
    690                 695                 700

Glu Val Gly Tyr Tyr Asn Asp Pro Val Ala Val Phe Asp Phe Ala Ser
705                 710                 715                 720

Leu Tyr Pro Ser Ile Ile Met Ala His Asn Leu Cys Tyr Ser Thr Leu
                725                 730                 735

Leu Val Pro Gly Gly Glu Tyr Pro Val Asp Pro Ala Asp Val Tyr Ser
            740                 745                 750

Val Thr Leu Glu Asn Gly Val Thr His Arg Phe Val Arg Ala Ser Val
```

```
        755                 760                 765

Arg Val Ser Val Leu Ser Glu Leu Leu Asn Lys Trp Val Ser Gln Arg
    770                 775                 780

Arg Ala Val Arg Glu Cys Met Arg Glu Cys Gln Asp Pro Val Arg Arg
785                 790                 795                 800

Met Leu Leu Asp Lys Glu Gln Met Ala Leu Lys Val Thr Cys Asn Ala
                805                 810                 815

Phe Tyr Gly Phe Thr Gly Val Val Asn Gly Met Met Pro Cys Leu Pro
            820                 825                 830

Ile Ala Ala Ser Ile Thr Arg Ile Gly Arg Asp Met Leu Glu Arg Thr
        835                 840                 845

Ala Arg Phe Ile Lys Asp Asn Phe Ser Glu Pro Cys Phe Leu His Asn
    850                 855                 860

Phe Phe Asn Gln Glu Asp Tyr Val Val Gly Thr Arg Glu Gly Asp Ser
865                 870                 875                 880

Glu Glu Ser Ser Ala Leu Pro Glu Gly Leu Glu Thr Ser Ser Gly Gly
                885                 890                 895

Ser Asn Glu Arg Arg Val Glu Ala Arg Val Ile Tyr Gly Asp Thr Asp
            900                 905                 910

Ser Val Phe Val Arg Phe Arg Gly Leu Thr Pro Gln Ala Leu Val Ala
        915                 920                 925

Arg Gly Pro Ser Leu Ala His Tyr Val Thr Ala Cys Leu Phe Val Glu
    930                 935                 940

Pro Val Lys Leu Glu Phe Glu Lys Val Phe Val Ser Leu Met Met Ile
945                 950                 955                 960

Cys Lys Lys Arg Tyr Ile Gly Lys Val Glu Gly Ala Ser Gly Leu Ser
                965                 970                 975

Met Lys Gly Val Asp Leu Val Arg Lys Thr Ala Cys Glu Phe Val Lys
            980                 985                 990

Gly Val Thr Arg Asp Val Leu Ser  Leu Leu Phe Glu Asp  Arg Glu Val
        995                 1000                1005

Ser Glu  Ala Ala Val Arg Leu  Ser Arg Leu Ser Leu  Asp Glu Val
    1010                1015                1020

Lys Lys  Tyr Gly Val Pro Arg  Gly Phe Trp Arg Ile  Leu Arg Arg
    1025                1030                1035

Leu Val  Gln Ala Arg Asp Asp  Leu Tyr Leu His Arg  Val Arg Val
    1040                1045                1050

Glu Asp  Leu Val Leu Ser Ser  Val Leu Ser Lys Asp  Ile Ser Leu
    1055                1060                1065

Tyr Arg  Gln Ser Asn Leu Pro  His Ile Ala Val Ile  Lys Arg Leu
    1070                1075                1080
```

```
Ala Ala  Arg Ser Glu Glu Leu  Pro Ser Val Gly Asp  Arg Val Phe
    1085                 1090                 1095

Tyr Val  Leu Thr Ala Pro Gly  Val Arg Thr Ala Pro  Gln Gly Ser
    1100                 1105                 1110

Ser Asp  Asn Gly Asp Ser Val  Thr Ala Gly Val Val  Ser Arg Ser
    1115                 1120                 1125

Asp Ala  Ile Asp Gly Thr Asp  Asp Asp Ala Asp Gly  Gly Gly Val
    1130                 1135                 1140

Glu Glu  Ser Asn Arg Arg Gly  Gly Glu Pro Ala Lys  Lys Arg Ala
    1145                 1150                 1155

Arg Lys  Pro Pro Ser Ala Val  Cys Asn Tyr Glu Val  Ala Glu Asp
    1160                 1165                 1170

Pro Ser  Tyr Val Arg Glu His  Gly Val Pro Ile His  Ala Asp Lys
    1175                 1180                 1185

Tyr Phe  Glu Gln Val Leu Lys  Ala Val Thr Asn Val  Leu Ser Pro
    1190                 1195                 1200

Val Phe  Pro Gly Gly Glu Thr  Ala Arg Lys Asp Lys  Phe Leu His
    1205                 1210                 1215

Met Val  Leu Pro Arg Arg Leu  His Leu Glu Pro Ala  Phe Leu Pro
    1220                 1225                 1230

Tyr Ser  Val Lys Ala His Glu  Cys Cys
    1235                 1240
```

<210> 14
<211> 1238
<212> PRT
<213> herpes simplex

<400> 14

```
Met Phe Cys Ala Ala Gly Gly Pro Thr Ser Pro Gly Gly Lys Ser Ala
1               5                  10                  15

Ala Arg Ala Ala Ser Gly Phe Phe Ala Pro His Asn Pro Arg Gly Ala
            20                  25                  30

Thr Gln Thr Ala Pro Pro Pro Cys Arg Arg Gln Asn Phe Tyr Asn Pro
        35                  40                  45

His Leu Ala Gln Thr Gly Thr Gln Pro Lys Ala Pro Gly Pro Ala Gln
    50                  55                  60

Arg His Thr Tyr Tyr Ser Glu Cys Asp Glu Phe Arg Phe Ile Ala Pro
65                  70                  75                  80

Arg Ser Leu Asp Glu Asp Ala Pro Ala Glu Gln Arg Thr Gly Val His
                85                  90                  95

Asp Gly Arg Leu Arg Arg Ala Pro Lys Val Tyr Cys Gly Gly Asp Glu
            100                 105                 110

Arg Asp Val Leu Arg Val Gly Pro Glu Gly Phe Trp Pro Arg Arg Leu
```

```
        115                 120                 125

Arg Leu Trp Gly Gly Ala Asp His Ala Pro Lys Gly Phe Asp Pro Thr
    130                 135                 140

Val Thr Val Phe His Val Tyr Asp Ile Leu Glu His Val Glu His Ala
145                 150                 155                 160

Tyr Ser Met Arg Ala Ala Gln Leu His Glu Arg Phe Met Asp Ala Ile
                165                 170                 175

Thr Pro Ala Gly Thr Val Ile Thr Leu Leu Gly Leu Thr Pro Glu Gly
            180                 185                 190

His Arg Val Ala Val His Val Tyr Gly Thr Arg Gln Tyr Phe Tyr Met
        195                 200                 205

Asn Lys Ala Glu Val Asp Arg His Leu Gln Cys Arg Ala Pro Arg Asp
    210                 215                 220

Leu Cys Glu Arg Leu Ala Ala Ala Leu Arg Glu Ser Pro Gly Ala Ser
225                 230                 235                 240

Phe Arg Gly Ile Ser Ala Asp His Phe Glu Ala Glu Val Val Glu Arg
                245                 250                 255

Ala Asp Val Tyr Tyr Tyr Glu Thr Arg Pro Thr Leu Tyr Tyr Arg Val
            260                 265                 270

Phe Val Arg Ser Gly Arg Ala Leu Ala Tyr Leu Cys Asp Asn Phe Cys
        275                 280                 285

Pro Ala Ile Arg Lys Tyr Glu Gly Gly Val Asp Ala Thr Thr Arg Phe
    290                 295                 300

Ile Leu Asp Asn Pro Gly Phe Val Thr Phe Gly Trp Tyr Arg Leu Lys
305                 310                 315                 320

Pro Gly Arg Gly Asn Ala Pro Ala Gln Pro Arg Pro Pro Thr Ala Phe
                325                 330                 335

Gly Thr Ser Ser Asp Val Glu Phe Asn Cys Thr Ala Asp Asn Leu Ala
            340                 345                 350

Val Glu Gly Ala Met Cys Asp Leu Pro Ala Tyr Lys Leu Met Cys Phe
        355                 360                 365

Asp Ile Glu Cys Lys Ala Gly Gly Glu Asp Glu Leu Ala Phe Pro Val
    370                 375                 380

Ala Glu Arg Pro Glu Asp Leu Val Ile Gln Ile Ser Cys Leu Leu Tyr
385                 390                 395                 400

Asp Leu Ser Thr Thr Ala Leu Glu His Ile Leu Leu Phe Ser Leu Gly
                405                 410                 415

Ser Cys Asp Leu Pro Glu Ser His Leu Ser Asp Leu Ala Ser Arg Gly
            420                 425                 430

Leu Pro Ala Pro Val Val Leu Glu Phe Asp Ser Glu Phe Glu Met Leu
        435                 440                 445
```

```
Leu Ala Phe Met Thr Phe Val Lys Gln Tyr Gly Pro Glu Phe Val Thr
    450                 455                 460

Gly Tyr Asn Ile Ile Asn Phe Asp Trp Pro Phe Val Leu Thr Lys Leu
465                 470                 475                 480

Thr Glu Ile Tyr Lys Val Pro Leu Asp Gly Tyr Gly Arg Met Asn Gly
                485                 490                 495

Arg Gly Val Phe Arg Val Trp Asp Ile Gly Gln Ser His Phe Gln Lys
            500                 505                 510

Arg Ser Lys Ile Lys Val Asn Gly Met Val Asn Ile Asp Met Tyr Gly
        515                 520                 525

Ile Ile Thr Asp Lys Val Lys Leu Ser Ser Tyr Lys Leu Asn Ala Val
    530                 535                 540

Ala Glu Ala Val Leu Lys Asp Lys Lys Lys Asp Leu Ser Tyr Arg Asp
545                 550                 555                 560

Ile Pro Ala Tyr Tyr Ala Ser Gly Pro Ala Gln Arg Gly Val Ile Gly
                565                 570                 575

Glu Tyr Cys Val Gln Asp Ser Leu Leu Val Gly Gln Leu Phe Phe Lys
            580                 585                 590

Phe Leu Pro His Leu Glu Leu Ser Ala Val Ala Arg Leu Ala Gly Ile
        595                 600                 605

Asn Ile Thr Arg Thr Ile Tyr Asp Gly Gln Gln Ile Arg Val Phe Thr
    610                 615                 620

Cys Leu Leu Arg Leu Ala Gly Gln Lys Gly Phe Ile Leu Pro Asp Thr
625                 630                 635                 640

Gln Gly Arg Phe Arg Gly Leu Asp Lys Glu Ala Pro Lys Arg Pro Ala
                645                 650                 655

Val Pro Arg Gly Glu Gly Glu Arg Pro Gly Asp Gly Asn Gly Asp Glu
            660                 665                 670

Asp Lys Asp Asp Asp Glu Asp Glu Asp Gly Asp Glu Arg Glu Glu Val
        675                 680                 685

Ala Arg Glu Thr Gly Gly Arg His Val Gly Tyr Gln Gly Ala Arg Val
    690                 695                 700

Leu Asp Pro Thr Ser Gly Phe His Val Asp Pro Val Val Val Phe Asp
705                 710                 715                 720

Phe Ala Ser Leu Tyr Pro Ser Ile Ile Gln Ala His Asn Leu Cys Phe
                725                 730                 735

Ser Thr Leu Ser Leu Arg Pro Glu Ala Val Ala His Leu Glu Ala Asp
            740                 745                 750

Arg Asp Tyr Leu Glu Ile Glu Val Gly Gly Arg Arg Leu Phe Phe Val
        755                 760                 765

Lys Ala His Val Arg Glu Ser Leu Leu Ser Ile Leu Leu Arg Asp Trp
    770                 775                 780
```

```
Leu Ala Met Arg Lys Gln Ile Arg Ser Arg Ile Pro Gln Ser Thr Pro
785                 790                 795                 800

Glu Glu Ala Val Leu Leu Asp Lys Gln Gln Ala Ala Ile Lys Val Val
                805                 810                 815

Cys Asn Ser Val Tyr Gly Phe Thr Gly Val Gln His Gly Leu Leu Pro
            820                 825                 830

Cys Leu His Val Ala Ala Thr Val Thr Thr Ile Gly Arg Glu Met Leu
        835                 840                 845

Leu Ala Thr Arg Ala Tyr Val His Ala Arg Trp Ala Glu Phe Asp Gln
    850                 855                 860

Leu Leu Ala Asp Phe Pro Glu Ala Ala Gly Met Arg Ala Pro Gly Pro
865                 870                 875                 880

Tyr Ser Met Arg Ile Ile Tyr Gly Asp Thr Asp Ser Ile Phe Val Leu
                885                 890                 895

Cys Arg Gly Leu Thr Ala Ala Gly Leu Val Ala Met Gly Asp Lys Met
            900                 905                 910

Ala Ser His Ile Ser Arg Ala Leu Phe Leu Pro Pro Ile Lys Leu Glu
        915                 920                 925

Cys Glu Lys Thr Phe Thr Lys Leu Leu Leu Ile Ala Lys Lys Lys Tyr
    930                 935                 940

Ile Gly Val Ile Cys Gly Gly Lys Met Leu Ile Lys Gly Val Asp Leu
945                 950                 955                 960

Val Arg Lys Asn Asn Cys Ala Phe Ile Asn Arg Thr Ser Arg Ala Leu
                965                 970                 975

Val Asp Leu Leu Phe Tyr Asp Asp Thr Val Ser Gly Ala Ala Ala Ala
            980                 985                 990

Leu Ala Glu Arg Pro Ala Glu Glu  Trp Leu Ala Arg Pro  Leu Pro Glu
        995                 1000                1005

Gly Leu  Gln Ala Phe Gly Ala  Val Leu Val Asp Ala  His Arg Arg
    1010                1015                1020

Ile Thr  Asp Pro Glu Arg Asp  Ile Gln Asp Phe Val  Leu Thr Ala
    1025                1030                1035

Glu Leu  Ser Arg His Pro Arg  Ala Tyr Thr Asn Lys  Arg Leu Ala
    1040                1045                1050

His Leu  Thr Val Tyr Tyr Lys  Leu Met Ala Arg Arg  Ala Gln Val
    1055                1060                1065

Pro Ser  Ile Lys Asp Arg Ile  Pro Tyr Val Ile Val  Ala Gln Thr
    1070                1075                1080

Arg Glu  Val Glu Glu Thr Val  Ala Arg Leu Ala Ala  Leu Arg Glu
    1085                1090                1095

Leu Asp  Ala Ala Ala Pro Gly  Asp Glu Pro Ala Pro  Pro Ala Ala
```

```
    1100                1105                1110

Leu Pro  Ser Pro Ala Lys Arg  Pro Arg Glu Thr Pro  Ser His Ala
    1115                1120                1125

Asp Pro  Pro Gly Gly Ala Ser  Lys Pro Arg Lys Leu  Leu Val Ser
    1130                1135                1140

Glu Leu  Ala Glu Asp Pro Gly  Tyr Ala Ile Ala Arg  Gly Val Pro
    1145                1150                1155

Leu Asn  Thr Asp Tyr Tyr Phe  Ser His Leu Leu Gly  Ala Ala Cys
    1160                1165                1170

Val Thr  Phe Lys Ala Leu Phe  Gly Asn Asn Ala Lys  Ile Thr Glu
    1175                1180                1185

Ser Leu  Leu Lys Arg Phe Ile  Pro Glu Thr Trp His  Pro Pro Asp
    1190                1195                1200

Asp Val  Ala Ala Arg Leu Arg  Ala Ala Gly Phe Gly  Pro Ala Gly
    1205                1210                1215

Ala Gly  Ala Thr Ala Glu Glu  Thr Arg Arg Met Leu  His Arg Ala
    1220                1225                1230

Phe Asp  Thr Leu Ala
    1235
```

<210> 15
<211> 1240
<212> PRT
<213> herpes simplex

<400> 15

```
Met Phe Cys Ala Ala Gly Gly Pro Ala Ser Pro Gly Gly Lys Ser Ala
1               5                   10                  15

Ala Arg Ala Ala Ser Gly Phe Phe Ala Pro His Asn Pro Arg Gly Ala
            20                  25                  30

Thr Gln Thr Ala Pro Pro Pro Cys Arg Arg Gln Asn Phe Tyr Asn Pro
        35                  40                  45

His Leu Ala Gln Thr Gly Thr Gln Pro Lys Ala Pro Gly Pro Ala Gln
    50                  55                  60

Arg His Thr Tyr Tyr Ser Glu Cys Asp Glu Phe Arg Phe Ile Ala Pro
65                  70                  75                  80

Arg Ser Leu Asp Glu Asp Ala Pro Ala Glu Gln Arg Thr Gly Val His
                85                  90                  95

Asp Gly Arg Leu Arg Arg Ala Pro Lys Val Tyr Cys Gly Gly Asp Glu
            100                 105                 110

Arg Asp Val Leu Arg Val Gly Pro Glu Gly Phe Trp Pro Arg Arg Leu
        115                 120                 125

Arg Leu Trp Gly Gly Ala Asp His Ala Pro Glu Gly Phe Asp Pro Thr
    130                 135                 140
```

```
Val Thr Val Phe His Val Tyr Asp Ile Leu Glu His Val Glu His Ala
145                 150                 155                 160

Tyr Ser Met Arg Ala Ala Gln Leu His Glu Arg Phe Met Asp Ala Ile
                165                 170                 175

Thr Pro Ala Gly Thr Val Ile Thr Leu Leu Gly Leu Thr Pro Glu Gly
            180                 185                 190

His Arg Val Ala Val His Val Tyr Gly Thr Arg Gln Tyr Phe Tyr Met
        195                 200                 205

Asn Lys Ala Glu Val Asp Arg His Leu Gln Cys Arg Ala Pro Arg Asp
    210                 215                 220

Leu Cys Glu Arg Leu Ala Ala Ala Leu Arg Glu Ser Pro Gly Ala Ser
225                 230                 235                 240

Phe Arg Gly Ile Ser Ala Asp His Phe Glu Ala Glu Val Val Glu Arg
                245                 250                 255

Ala Asp Val Tyr Tyr Tyr Glu Thr Arg Pro Thr Leu Tyr Tyr Arg Val
            260                 265                 270

Phe Val Arg Ser Gly Arg Ala Leu Ala Tyr Leu Cys Asp Asn Phe Cys
        275                 280                 285

Pro Ala Ile Arg Lys Tyr Glu Gly Gly Val Asp Ala Thr Thr Arg Phe
    290                 295                 300

Ile Leu Asp Asn Pro Gly Phe Val Thr Phe Gly Trp Tyr Arg Leu Lys
305                 310                 315                 320

Pro Gly Arg Gly Asn Ala Pro Ala Gln Pro Arg Pro Pro Thr Ala Phe
                325                 330                 335

Gly Thr Ser Ser Asp Val Glu Phe Asn Cys Thr Ala Asp Asn Leu Ala
            340                 345                 350

Val Glu Gly Ala Met Cys Asp Leu Pro Ala Tyr Lys Leu Met Cys Phe
        355                 360                 365

Asp Ile Glu Cys Lys Ala Gly Gly Glu Asp Glu Leu Ala Phe Pro Val
    370                 375                 380

Ala Glu Arg Pro Glu Asp Leu Val Ile Gln Ile Ser Cys Leu Leu Tyr
385                 390                 395                 400

Asp Leu Ser Thr Thr Ala Leu Glu His Ile Leu Leu Phe Ser Leu Gly
                405                 410                 415

Ser Cys Asp Leu Pro Glu Ser His Leu Ser Asp Leu Ala Ser Arg Gly
            420                 425                 430

Leu Pro Ala Pro Val Val Leu Glu Phe Asp Ser Glu Phe Glu Met Leu
        435                 440                 445

Leu Ala Phe Met Thr Phe Val Lys Gln Tyr Gly Pro Glu Phe Val Thr
    450                 455                 460

Gly Tyr Asn Ile Ile Asn Phe Asp Trp Pro Phe Val Leu Thr Lys Leu
```

```
465                 470                 475                 480

Thr Glu Ile Tyr Lys Val Pro Leu Asp Gly Tyr Gly Arg Met Asn Gly
                485                 490                 495

Arg Gly Val Phe Arg Val Trp Asp Ile Gly Gln Ser His Phe Gln Lys
            500                 505                 510

Arg Ser Lys Ile Lys Val Asn Gly Met Val Asn Ile Asp Met Tyr Gly
        515                 520                 525

Ile Ile Thr Asp Lys Val Lys Leu Ser Ser Tyr Lys Leu Asn Ala Val
    530                 535                 540

Ala Glu Ala Val Leu Lys Asp Lys Lys Lys Asp Leu Ser Tyr Arg Asp
545                 550                 555                 560

Ile Pro Ala Tyr Tyr Ala Ser Gly Pro Ala Gln Arg Gly Val Ile Gly
                565                 570                 575

Glu Tyr Cys Val Gln Asp Ser Leu Leu Val Gly Gln Leu Phe Phe Lys
            580                 585                 590

Phe Leu Pro His Leu Glu Leu Ser Ala Val Ala Arg Leu Ala Gly Ile
        595                 600                 605

Asn Ile Thr Arg Thr Ile Tyr Asp Gly Gln Gln Ile Arg Val Phe Thr
    610                 615                 620

Cys Leu Leu Arg Leu Ala Gly Gln Lys Gly Phe Ile Leu Pro Asp Thr
625                 630                 635                 640

Gln Gly Arg Phe Arg Gly Leu Asp Lys Glu Ala Pro Lys Arg Pro Ala
                645                 650                 655

Val Pro Arg Gly Glu Gly Glu Arg Pro Gly Asp Gly Asn Gly Asp Glu
            660                 665                 670

Asp Lys Asp Asp Asp Glu Asp Gly Asp Glu Asp Gly Asp Glu Arg Glu
        675                 680                 685

Glu Val Ala Arg Glu Thr Gly Gly Arg His Val Gly Tyr Gln Gly Ala
    690                 695                 700

Arg Val Leu Asp Pro Thr Ser Gly Phe His Val Asp Pro Val Val Val
705                 710                 715                 720

Phe Asp Phe Ala Ser Leu Tyr Pro Ser Ile Ile Gln Ala His Asn Leu
                725                 730                 735

Cys Phe Ser Thr Leu Ser Leu Arg Pro Glu Ala Val Ala His Leu Glu
            740                 745                 750

Ala Asp Arg Asp Tyr Leu Glu Ile Glu Val Gly Gly Arg Arg Leu Phe
        755                 760                 765

Phe Val Lys Ala His Val Arg Glu Ser Leu Leu Ser Ile Leu Leu Arg
    770                 775                 780

Asp Trp Leu Ala Met Arg Lys Gln Ile Arg Ser Arg Ile Pro Gln Ser
785                 790                 795                 800
```

```
Pro Pro Glu Glu Ala Val Leu Leu Asp Lys Gln Gln Ala Ala Ile Lys
                805                 810                 815

Val Val Cys Asn Ser Val Tyr Gly Phe Thr Gly Val Gln His Gly Leu
            820                 825                 830

Leu Pro Cys Leu His Val Ala Ala Thr Val Thr Thr Ile Gly Arg Glu
        835                 840                 845

Met Leu Leu Ala Thr Arg Ala Tyr Val His Ala Arg Trp Ala Glu Phe
    850                 855                 860

Asp Gln Leu Leu Ala Asp Phe Pro Glu Ala Ala Gly Met Arg Ala Pro
865                 870                 875                 880

Gly Pro Tyr Ser Met Arg Ile Ile Tyr Gly Asp Thr Asp Ser Ile Phe
                885                 890                 895

Val Leu Cys Arg Gly Leu Thr Ala Ala Gly Leu Val Ala Met Gly Asp
            900                 905                 910

Lys Met Ala Ser His Ile Ser Arg Ala Leu Phe Leu Pro Pro Ile Lys
        915                 920                 925

Leu Glu Cys Glu Lys Thr Phe Thr Lys Leu Leu Leu Ile Ala Lys Lys
    930                 935                 940

Lys Tyr Ile Gly Val Ile Cys Gly Gly Lys Met Leu Ile Lys Gly Val
945                 950                 955                 960

Asp Leu Val Arg Lys Asn Asn Cys Ala Phe Ile Asn Arg Thr Ser Arg
                965                 970                 975

Ala Leu Val Asp Leu Leu Phe Tyr Asp Asp Thr Val Ser Gly Ala Ala
            980                 985                 990

Ala Ala Leu Ala Glu Arg Pro Ala  Glu Glu Trp Leu Ala  Arg Pro Leu
        995                 1000                1005

Pro Glu  Gly Leu Gln Ala Phe  Gly Ala Val Leu Val  Asp Ala His
    1010                1015                1020

Arg Arg  Ile Thr Asp Pro Glu  Arg Asp Ile Gln Asp  Phe Val Leu
    1025                1030                1035

Thr Ala  Glu Leu Ser Arg His  Pro Arg Ala Tyr Thr  Asn Lys Arg
    1040                1045                1050

Leu Ala  His Leu Thr Val Tyr  Tyr Lys Leu Met Ala  Arg Arg Ala
    1055                1060                1065

Gln Val  Pro Ser Ile Lys Asp  Arg Ile Pro Tyr Val  Ile Val Ala
    1070                1075                1080

Gln Thr  Arg Glu Val Glu Glu  Thr Val Ala Arg Leu  Ala Ala Leu
    1085                1090                1095

Arg Glu  Leu Asp Ala Ala Ala  Pro Gly Asp Glu Pro  Ala Pro Pro
    1100                1105                1110

Ala Ala  Leu Pro Ser Pro Ala  Lys Arg Pro Arg Glu  Thr Pro Ser
    1115                1120                1125
```

```
His Ala  Asp Pro Pro Gly Gly  Ala Ser Lys Pro Arg  Lys Leu Leu
    1130                 1135                 1140

Val Ser  Glu Leu Ala Glu Asp  Pro Gly Tyr Ala Ile  Ala Arg Gly
    1145                 1150                 1155

Val Pro  Leu Asn Thr Asp Tyr  Tyr Phe Ser His Leu  Leu Gly Ala
    1160                 1165                 1170

Ala Cys  Val Thr Phe Lys Ala  Leu Phe Gly Asn Asn  Ala Lys Ile
    1175                 1180                 1185

Thr Glu  Ser Leu Leu Lys Arg  Phe Ile Pro Glu Thr  Trp His Pro
    1190                 1195                 1200

Pro Asp  Asp Val Ala Ala Arg  Leu Arg Ala Ala Gly  Phe Gly Pro
    1205                 1210                 1215

Ala Gly  Ala Gly Ala Thr Ala  Glu Glu Thr Arg Arg  Met Leu His
    1220                 1225                 1230

Arg Ala  Phe Asp Thr Leu Ala
    1235                 1240
```

<210> 16
<211> 1235
<212> PRT
<213> herpes simplex

<400> 16

```
Met Phe Ser Gly Gly Gly Gly Pro Leu Ser Pro Gly Gly Lys Ser Ala
1               5                  10                  15

Ala Arg Ala Ala Ser Gly Phe Phe Ala Pro Ala Gly Pro Arg Gly Ala
            20                  25                  30

Gly Arg Gly Pro Pro Pro Cys Leu Arg Gln Asn Phe Tyr Asn Pro Tyr
        35                  40                  45

Leu Ala Pro Val Gly Thr Gln Gln Lys Pro Thr Gly Pro Thr Gln Arg
    50                  55                  60

His Thr Tyr Tyr Ser Glu Cys Asp Glu Phe Arg Phe Ile Ala Pro Arg
65                  70                  75                  80

Val Leu Asp Glu Asp Ala Pro Pro Glu Lys Arg Ala Gly Val His Asp
                85                  90                  95

Gly His Leu Lys Arg Ala Pro Lys Val Tyr Cys Gly Gly Asp Glu Arg
            100                 105                 110

Asp Val Leu Arg Val Gly Ser Gly Gly Phe Trp Pro Arg Arg Ser Arg
        115                 120                 125

Leu Trp Gly Gly Val Asp His Ala Pro Ala Gly Phe Asn Pro Thr Val
    130                 135                 140

Thr Val Phe His Val Tyr Asp Ile Leu Glu Asn Val Glu His Ala Tyr
145                 150                 155                 160
```

```
Gly Met Arg Ala Ala Gln Phe His Ala Arg Phe Met Asp Ala Ile Thr
                165                 170                 175

Pro Thr Gly Thr Val Ile Thr Leu Leu Gly Leu Thr Pro Glu Gly His
            180                 185                 190

Arg Val Ala Val His Val Tyr Gly Thr Arg Gln Tyr Phe Tyr Met Asn
        195                 200                 205

Lys Glu Glu Val Asp Arg His Leu Gln Cys Arg Ala Pro Arg Asp Leu
    210                 215                 220

Cys Glu Arg Met Ala Ala Ala Leu Arg Glu Ser Pro Gly Ala Ser Phe
225                 230                 235                 240

Arg Gly Ile Ser Ala Asp His Phe Glu Ala Glu Val Val Glu Arg Thr
                245                 250                 255

Asp Val Tyr Tyr Tyr Glu Thr Arg Pro Ala Leu Phe Tyr Arg Val Tyr
            260                 265                 270

Val Arg Ser Gly Arg Val Leu Ser Tyr Leu Cys Asp Asn Phe Cys Pro
        275                 280                 285

Ala Ile Lys Lys Tyr Glu Gly Gly Val Asp Ala Thr Thr Arg Phe Ile
    290                 295                 300

Leu Asp Asn Pro Gly Phe Val Thr Phe Gly Trp Tyr Arg Leu Lys Pro
305                 310                 315                 320

Gly Arg Asn Asn Thr Leu Ala Gln Pro Arg Ala Pro Met Ala Phe Gly
                325                 330                 335

Thr Ser Ser Asp Val Glu Phe Asn Cys Thr Ala Asp Asn Leu Ala Ile
            340                 345                 350

Glu Gly Gly Met Ser Asp Leu Pro Ala Tyr Lys Leu Met Cys Phe Asp
        355                 360                 365

Ile Glu Cys Lys Ala Gly Gly Glu Asp Glu Leu Ala Phe Pro Val Ala
    370                 375                 380

Gly His Pro Glu Asp Leu Val Ile Gln Ile Ser Cys Leu Leu Tyr Asp
385                 390                 395                 400

Leu Ser Thr Thr Ala Leu Glu His Val Leu Leu Phe Ser Leu Gly Ser
                405                 410                 415

Cys Asp Leu Pro Glu Ser His Leu Asn Glu Leu Ala Ala Arg Gly Leu
            420                 425                 430

Pro Thr Pro Val Val Leu Glu Phe Asp Ser Glu Phe Glu Met Leu Leu
        435                 440                 445

Ala Phe Met Thr Leu Val Lys Gln Tyr Gly Pro Glu Phe Val Thr Gly
    450                 455                 460

Tyr Asn Ile Ile Asn Phe Asp Trp Pro Phe Leu Leu Ala Lys Leu Thr
465                 470                 475                 480

Asp Ile Tyr Lys Val Pro Leu Asp Gly Tyr Gly Arg Met Asn Gly Arg
                485                 490                 495
```

```
Gly Val Phe Arg Val Trp Asp Ile Gly Gln Ser His Phe Gln Lys Arg
            500                 505                 510

Ser Lys Ile Lys Val Asn Gly Met Val Asn Ile Asp Met Tyr Gly Ile
        515                 520                 525

Ile Thr Asp Lys Ile Lys Leu Ser Ser Tyr Lys Leu Asn Ala Val Ala
    530                 535                 540

Glu Ala Val Leu Lys Asp Lys Lys Lys Asp Leu Ser Tyr Arg Asp Ile
545                 550                 555                 560

Pro Ala Tyr Tyr Ala Ala Gly Pro Ala Gln Arg Gly Val Ile Gly Glu
                565                 570                 575

Tyr Cys Ile Gln Asp Ser Leu Leu Val Gly Gln Leu Phe Phe Lys Phe
            580                 585                 590

Leu Pro His Leu Glu Leu Ser Ala Val Ala Arg Leu Ala Gly Ile Asn
        595                 600                 605

Ile Thr Arg Thr Ile Tyr Asp Gly Gln Gln Ile Arg Val Phe Thr Cys
    610                 615                 620

Leu Leu Arg Leu Ala Asp Gln Lys Gly Phe Ile Leu Pro Asp Thr Gln
625                 630                 635                 640

Gly Arg Phe Arg Gly Ala Gly Gly Glu Ala Pro Lys Arg Pro Ala Ala
                645                 650                 655

Ala Arg Glu Asp Glu Glu Arg Pro Glu Glu Glu Gly Glu Asp Glu Asp
            660                 665                 670

Glu Arg Glu Glu Gly Gly Gly Glu Arg Glu Pro Glu Gly Ala Arg Glu
        675                 680                 685

Thr Ala Gly Arg His Val Gly Tyr Gln Gly Ala Arg Val Leu Asp Pro
    690                 695                 700

Thr Ser Gly Phe His Val Asn Pro Val Val Val Phe Asp Phe Ala Ser
705                 710                 715                 720

Leu Tyr Pro Ser Ile Ile Gln Ala His Asn Leu Cys Phe Ser Thr Leu
                725                 730                 735

Ser Leu Arg Ala Asp Ala Val Ala His Leu Glu Ala Gly Lys Asp Tyr
            740                 745                 750

Leu Glu Ile Glu Val Gly Gly Arg Arg Leu Phe Phe Val Lys Ala His
        755                 760                 765

Val Arg Glu Ser Leu Leu Ser Ile Leu Leu Arg Asp Trp Leu Ala Met
    770                 775                 780

Arg Lys Gln Ile Arg Ser Arg Ile Pro Gln Ser Ser Pro Glu Glu Ala
785                 790                 795                 800

Val Leu Leu Asp Lys Gln Gln Ala Ala Ile Lys Val Val Cys Asn Ser
                805                 810                 815

Val Tyr Gly Phe Thr Gly Val Gln His Gly Leu Leu Pro Cys Leu His
```

```
          820                 825                 830

Val Ala Ala Thr Val Thr Thr Ile Gly Arg Glu Met Leu Leu Ala Thr
        835                 840                 845

Arg Glu Tyr Val His Ala Arg Trp Ala Ala Phe Glu Gln Leu Leu Ala
    850                 855                 860

Asp Phe Pro Glu Ala Ala Asp Met Arg Ala Pro Gly Pro Tyr Ser Met
865                 870                 875                 880

Arg Ile Ile Tyr Gly Asp Thr Asp Ser Ile Phe Val Leu Cys Arg Gly
                885                 890                 895

Leu Thr Ala Ala Gly Leu Thr Ala Met Gly Asp Lys Met Ala Ser His
            900                 905                 910

Ile Ser Arg Ala Leu Phe Leu Pro Pro Ile Lys Leu Glu Cys Glu Lys
        915                 920                 925

Thr Phe Thr Lys Leu Leu Leu Ile Ala Lys Lys Lys Tyr Ile Gly Val
    930                 935                 940

Ile Tyr Gly Gly Lys Met Leu Ile Lys Gly Val Asp Leu Val Arg Lys
945                 950                 955                 960

Asn Asn Cys Ala Phe Ile Asn Arg Thr Ser Arg Ala Leu Val Asp Leu
                965                 970                 975

Leu Phe Tyr Asp Asp Thr Val Ser Gly Ala Ala Ala Ala Leu Ala Glu
            980                 985                 990

Arg Pro Ala Glu Glu Trp Leu Ala  Arg Pro Leu Pro Glu  Gly Leu Gln
        995                 1000                1005

Ala Phe  Gly Ala Val Leu Val  Asp Ala His Arg Arg  Ile Thr Asp
    1010                1015                1020

Pro Glu  Arg Asp Ile Gln Asp  Phe Val Leu Thr Ala  Glu Leu Ser
    1025                1030                1035

Arg His  Pro Arg Ala Tyr Thr  Asn Lys Arg Leu Ala  His Leu Thr
    1040                1045                1050

Val Tyr  Tyr Lys Leu Met Ala  Arg Arg Ala Gln Val  Pro Ser Ile
    1055                1060                1065

Lys Asp  Arg Ile Pro Tyr Val  Ile Val Ala Gln Thr  Arg Glu Val
    1070                1075                1080

Glu Glu  Thr Val Ala Arg Leu  Ala Ala Leu Arg Glu  Leu Asp Ala
    1085                1090                1095

Ala Ala  Pro Gly Asp Glu Pro  Ala Pro Pro Ala Ala  Leu Pro Ser
    1100                1105                1110

Pro Ala  Lys Arg Pro Arg Glu  Thr Pro Ser His Ala  Asp Pro Pro
    1115                1120                1125

Gly Gly  Ala Ser Lys Pro Arg  Lys Leu Leu Val Ser  Glu Leu Ala
    1130                1135                1140
```

```
Glu Asp  Pro Ala Tyr Ala Ile  Ala His Gly Val Ala  Leu Asn Thr
    1145                 1150                 1155

Asp Tyr  Tyr Phe Ser His Leu  Leu Gly Ala Ala Cys  Val Thr Phe
    1160                 1165                 1170

Lys Ala  Leu Phe Gly Asn Asn  Ala Lys Ile Thr Glu  Ser Leu Leu
    1175                 1180                 1185

Lys Arg  Phe Ile Pro Glu Val  Trp His Pro Pro Asp  Asp Val Ala
    1190                 1195                 1200

Ala Arg  Leu Arg Ala Ala Gly  Phe Gly Ala Val Gly  Ala Gly Ala
    1205                 1210                 1215

Thr Ala  Glu Glu Thr Arg Arg  Met Leu His Arg Ala  Phe Asp Thr
    1220                 1225                 1230

Leu Ala
    1235
```

<210> 17
<211> 1235
<212> PRT
<213> herpes simplex

<400> 17

```
Met Phe Ser Gly Gly Gly Gly Pro Leu Ser Pro Gly Gly Lys Ser Ala
1               5                  10                  15

Ala Arg Ala Ala Ser Gly Phe Phe Ala Pro Ala Gly Pro Arg Gly Ala
            20                  25                  30

Gly Arg Gly Pro Pro Pro Cys Leu Arg Gln Asn Phe Tyr Asn Pro Tyr
        35                  40                  45

Leu Ala Pro Val Gly Thr Gln Gln Lys Pro Thr Gly Pro Thr Gln Arg
    50                  55                  60

His Thr Tyr Tyr Ser Glu Cys Asp Glu Phe Arg Phe Ile Ala Pro Arg
65                  70                  75                  80

Val Leu Asp Glu Asp Ala Pro Pro Glu Lys Arg Ala Gly Val His Asp
                85                  90                  95

Gly His Leu Lys Arg Ala Pro Lys Val Tyr Cys Gly Gly Asp Glu Arg
            100                 105                 110

Asp Val Leu Arg Val Gly Ser Gly Gly Phe Trp Pro Arg Arg Ser Arg
        115                 120                 125

Leu Trp Gly Gly Val Asp His Ala Pro Ala Gly Phe Asn Pro Thr Val
    130                 135                 140

Thr Val Phe His Val Tyr Asp Ile Leu Glu Asn Val Glu His Ala Tyr
145                 150                 155                 160

Gly Met Arg Ala Ala Gln Phe His Ala Arg Phe Met Asp Ala Ile Thr
                165                 170                 175

Pro Thr Gly Thr Val Ile Thr Leu Leu Gly Leu Thr Pro Glu Gly His
```

```
            180                 185                 190

Arg Val Ala Val His Val Tyr Gly Thr Arg Gln Tyr Phe Tyr Met Asn
        195                 200                 205

Lys Glu Glu Val Asp Arg His Leu Gln Cys Arg Ala Pro Arg Asp Leu
    210                 215                 220

Cys Glu Arg Met Ala Ala Ala Leu Arg Glu Ser Pro Gly Ala Ser Phe
225                 230                 235                 240

Arg Gly Ile Ser Ala Asp His Phe Glu Ala Glu Val Val Glu Arg Thr
                245                 250                 255

Asp Val Tyr Tyr Tyr Glu Thr Arg Pro Ala Leu Phe Tyr Arg Val Tyr
            260                 265                 270

Val Arg Ser Gly Arg Val Leu Ser Tyr Leu Cys Asp Asn Phe Cys Pro
        275                 280                 285

Ala Ile Lys Lys Tyr Glu Gly Gly Val Asp Ala Thr Thr Arg Phe Ile
    290                 295                 300

Leu Asp Asn Pro Gly Phe Val Thr Phe Gly Trp Tyr Arg Leu Lys Pro
305                 310                 315                 320

Gly Arg Asn Asn Thr Leu Ala Gln Pro Arg Ala Pro Met Ala Phe Gly
                325                 330                 335

Thr Ser Ser Asp Val Glu Phe Asn Cys Thr Ala Asp Asn Leu Ala Ile
            340                 345                 350

Glu Gly Gly Met Ser Asp Leu Pro Ala Tyr Lys Leu Met Cys Phe Asp
        355                 360                 365

Ile Glu Cys Lys Ala Gly Gly Glu Asp Glu Leu Ala Phe Pro Val Ala
    370                 375                 380

Gly His Pro Glu Asp Leu Val Ile Gln Ile Ser Cys Leu Leu Tyr Asp
385                 390                 395                 400

Leu Ser Thr Thr Ala Leu Glu His Val Leu Leu Phe Ser Leu Gly Ser
                405                 410                 415

Cys Asp Leu Pro Glu Ser His Leu Asn Glu Leu Ala Ala Arg Gly Leu
            420                 425                 430

Pro Thr Pro Val Val Leu Glu Phe Asp Ser Glu Phe Glu Met Leu Leu
        435                 440                 445

Ala Phe Met Thr Leu Val Lys Gln Tyr Gly Pro Glu Phe Val Thr Gly
    450                 455                 460

Tyr Asn Ile Ile Asn Phe Asp Trp Pro Phe Leu Leu Ala Lys Leu Thr
465                 470                 475                 480

Asp Ile Tyr Lys Val Pro Leu Asp Gly Tyr Gly Arg Met Asn Gly Arg
                485                 490                 495

Gly Val Phe Arg Val Trp Asp Ile Gly Gln Ser His Phe Gln Lys Arg
            500                 505                 510
```

```
Ser Lys Ile Lys Val Asn Gly Met Val Asn Ile Asp Met Tyr Gly Ile
        515                 520                 525

Ile Thr Asp Lys Ile Lys Leu Ser Ser Tyr Lys Leu Asn Ala Val Ala
    530                 535                 540

Glu Ala Val Leu Lys Asp Lys Lys Lys Asp Leu Ser Tyr Arg Asp Ile
545                 550                 555                 560

Pro Ala Tyr Tyr Ala Ala Gly Pro Ala Gln Arg Gly Val Ile Gly Glu
                565                 570                 575

Tyr Cys Ile Gln Asp Ser Leu Leu Val Gly Gln Leu Phe Phe Lys Phe
            580                 585                 590

Leu Pro His Leu Glu Leu Ser Ala Val Ala Arg Leu Ala Gly Ile Asn
        595                 600                 605

Ile Thr Arg Thr Ile Tyr Asp Gly Gln Gln Ile Arg Val Phe Thr Cys
    610                 615                 620

Leu Leu Arg Leu Ala Asp Gln Lys Gly Phe Ile Leu Pro Asp Thr Gln
625                 630                 635                 640

Gly Arg Phe Arg Gly Ala Gly Gly Glu Ala Pro Lys Arg Pro Ala Ala
                645                 650                 655

Ala Arg Glu Asp Glu Glu Arg Pro Glu Glu Glu Gly Glu Asp Glu Asp
            660                 665                 670

Glu Arg Glu Glu Gly Gly Gly Glu Arg Glu Pro Glu Gly Ala Arg Glu
        675                 680                 685

Thr Ala Gly Arg His Val Gly Tyr Gln Gly Ala Arg Val Leu Asp Pro
    690                 695                 700

Ile Ser Gly Phe His Val Asn Pro Val Val Val Phe Asp Phe Ala Ser
705                 710                 715                 720

Leu Tyr Pro Ser Ile Ile Gln Ala His Asn Leu Cys Phe Ser Thr Leu
                725                 730                 735

Ser Leu Arg Ala Asp Ala Val Ala His Leu Glu Ala Gly Lys Asp Tyr
            740                 745                 750

Leu Glu Ile Glu Val Gly Gly Arg Arg Leu Phe Phe Val Lys Ala His
        755                 760                 765

Val Arg Glu Ser Leu Leu Ser Ile Leu Leu Arg Asp Trp Leu Ala Met
    770                 775                 780

Arg Lys Gln Ile Arg Ser Arg Ile Pro Gln Ser Ser Pro Glu Glu Ala
785                 790                 795                 800

Val Leu Leu Asp Lys Gln Gln Ala Ala Ile Lys Val Val Cys Asn Ser
                805                 810                 815

Val Tyr Gly Phe Thr Gly Val Gln His Gly Leu Leu Pro Cys Leu His
            820                 825                 830

Val Ala Ala Thr Val Thr Thr Ile Gly Arg Glu Met Leu Leu Ala Thr
        835                 840                 845
```

```
Arg Glu Tyr Val His Ala Arg Trp Ala Ala Phe Glu Gln Leu Leu Ala
    850                 855                 860

Asp Phe Pro Glu Ala Ala Asp Met Arg Ala Pro Gly Pro Tyr Ser Met
865                 870                 875                 880

Arg Ile Ile Tyr Gly Asp Thr Asp Ser Ile Phe Val Leu Cys Arg Gly
                885                 890                 895

Leu Thr Ala Ala Gly Leu Thr Ala Met Gly Asp Lys Met Ala Ser His
            900                 905                 910

Ile Ser Arg Ala Leu Phe Leu Pro Pro Ile Lys Leu Glu Cys Glu Lys
        915                 920                 925

Thr Phe Thr Lys Leu Leu Leu Ile Ala Lys Lys Lys Tyr Ile Gly Val
    930                 935                 940

Ile Tyr Gly Gly Lys Met Leu Ile Lys Gly Val Asp Leu Val Arg Lys
945                 950                 955                 960

Asn Asn Cys Ala Phe Ile Asn Arg Thr Ser Arg Ala Leu Val Asp Leu
                965                 970                 975

Leu Phe Tyr Asp Asp Thr Val Ser Gly Ala Ala Ala Ala Leu Ala Glu
            980                 985                 990

Arg Pro Ala Glu Glu Trp Leu Ala  Arg Pro Leu Pro Glu  Gly Leu Gln
        995                 1000                1005

Ala Phe  Gly Ala Val Leu Val  Asp Ala His Arg Arg  Ile Thr Asp
    1010                1015                1020

Pro Glu  Arg Asp Ile Gln Asp  Phe Val Leu Thr Ala  Glu Leu Ser
    1025                1030                1035

Arg His  Pro Arg Ala Tyr Thr  Asn Lys Arg Leu Ala  His Leu Thr
    1040                1045                1050

Val Tyr  Tyr Lys Leu Met Ala  Arg Arg Ala Gln Val  Pro Ser Ile
    1055                1060                1065

Lys Asp  Arg Ile Pro Tyr Val  Ile Val Ala Gln Thr  Arg Glu Val
    1070                1075                1080

Glu Glu  Thr Val Ala Arg Leu  Ala Ala Leu Arg Glu  Leu Asp Ala
    1085                1090                1095

Ala Ala  Pro Gly Asp Glu Pro  Ala Pro Pro Ala Ala  Leu Pro Ser
    1100                1105                1110

Pro Ala  Lys Arg Pro Arg Glu  Thr Pro Ser Pro Ala  Asp Pro Pro
    1115                1120                1125

Gly Gly  Ala Ser Lys Pro Arg  Lys Leu Leu Val Ser  Glu Leu Ala
    1130                1135                1140

Glu Asp  Pro Ala Tyr Ala Ile  Ala His Gly Val Ala  Leu Asn Thr
    1145                1150                1155

Asp Tyr  Tyr Phe Ser His Leu  Leu Gly Ala Ala Cys  Val Thr Phe
```

1160 1165 1170

Lys Ala Leu Phe Gly Asn Asn Ala Lys Ile Thr Glu Ser Leu Leu
1175 1180 1185

Lys Arg Phe Ile Pro Glu Val Trp His Pro Pro Asp Asp Val Thr
1190 1195 1200

Ala Arg Leu Arg Ala Ala Gly Phe Gly Ala Val Gly Ala Gly Ala
1205 1210 1215

Thr Ala Glu Glu Thr Arg Arg Met Leu His Arg Ala Phe Asp Thr
1220 1225 1230

Leu Ala
1235

<210> 18
<211> 1235
<212> PRT
<213> herpes simplex

<400> 18

Met Phe Ser Gly Gly Gly Gly Pro Leu Ser Pro Gly Gly Lys Ser Ala
1 5 10 15

Ala Arg Ala Ala Ser Gly Phe Phe Ala Pro Ala Gly Pro Arg Gly Ala
20 25 30

Gly Arg Gly Pro Pro Pro Cys Leu Arg Gln Asn Phe Tyr Asn Pro Tyr
35 40 45

Leu Ala Pro Val Gly Thr Gln Gln Lys Pro Thr Gly Pro Thr Gln Arg
50 55 60

His Thr Tyr Tyr Ser Glu Cys Asp Glu Phe Arg Phe Ile Ala Pro Arg
65 70 75 80

Val Leu Asp Glu Asp Ala Pro Pro Glu Lys Arg Ala Gly Val His Asp
85 90 95

Gly His Leu Lys Arg Ala Pro Lys Val Tyr Cys Gly Gly Asp Glu Arg
100 105 110

Asp Val Leu Arg Val Gly Ser Gly Gly Phe Trp Pro Arg Arg Ser Arg
115 120 125

Leu Trp Gly Gly Val Asp His Ala Pro Ala Gly Phe Asn Pro Thr Val
130 135 140

Thr Val Phe His Val Tyr Asp Ile Leu Glu Asn Val Glu His Ala Tyr
145 150 155 160

Gly Met Arg Ala Ala Gln Phe His Ala Arg Phe Met Asp Ala Ile Thr
165 170 175

Pro Thr Gly Thr Val Ile Thr Leu Leu Gly Leu Thr Pro Glu Gly His
180 185 190

Arg Val Ala Val His Val Tyr Gly Thr Arg Gln Tyr Phe Tyr Met Asn
195 200 205

```
Lys Glu Glu Val Asp Arg His Leu Gln Cys Arg Ala Pro Arg Asp Leu
    210                 215                 220

Cys Glu Arg Met Ala Ala Ala Leu Arg Glu Ser Pro Gly Ala Ser Phe
225                 230                 235                 240

Arg Gly Ile Ser Ala Asp His Phe Glu Ala Glu Val Val Glu Arg Thr
                245                 250                 255

Asp Val Tyr Tyr Tyr Glu Thr Arg Pro Ala Leu Phe Tyr Arg Val Tyr
            260                 265                 270

Val Arg Ser Gly Arg Val Leu Ser Tyr Leu Cys Asp Asn Phe Cys Pro
        275                 280                 285

Ala Ile Lys Lys Tyr Glu Gly Gly Val Asp Ala Thr Thr Arg Phe Ile
    290                 295                 300

Leu Asp Asn Pro Gly Phe Val Thr Phe Gly Trp Tyr Arg Leu Lys Pro
305                 310                 315                 320

Gly Arg Asn Asn Thr Leu Ala Gln Pro Arg Ala Pro Met Ala Phe Gly
                325                 330                 335

Thr Ser Ser Asp Val Glu Phe Asn Cys Thr Ala Asp Asn Leu Ala Ile
            340                 345                 350

Glu Gly Gly Met Ser Asp Leu Pro Ala Tyr Lys Leu Met Cys Phe Asp
        355                 360                 365

Ile Glu Cys Lys Ala Gly Gly Glu Asp Glu Leu Ala Phe Pro Val Ala
    370                 375                 380

Gly His Pro Glu Asp Leu Val Ile Gln Ile Ser Cys Leu Leu Tyr Asp
385                 390                 395                 400

Leu Ser Thr Thr Ala Leu Glu His Val Leu Leu Phe Ser Leu Gly Ser
                405                 410                 415

Cys Asp Leu Pro Glu Ser His Leu Asn Glu Leu Ala Ala Arg Gly Leu
            420                 425                 430

Pro Thr Pro Val Val Leu Glu Phe Asp Ser Glu Phe Glu Met Leu Leu
        435                 440                 445

Ala Phe Met Thr Leu Val Lys Gln Tyr Gly Pro Glu Phe Val Thr Gly
    450                 455                 460

Tyr Asn Ile Ile Asn Phe Asp Trp Pro Phe Leu Leu Ala Lys Leu Thr
465                 470                 475                 480

Asp Ile Tyr Lys Val Pro Leu Asp Gly Tyr Gly Arg Met Asn Gly Arg
                485                 490                 495

Gly Val Phe Arg Val Trp Asp Ile Gly Gln Ser His Phe Gln Lys Arg
            500                 505                 510

Ser Lys Ile Lys Val Asn Gly Met Val Asn Ile Asp Met Tyr Gly Ile
        515                 520                 525

Ile Thr Asp Lys Ile Lys Leu Ser Ser Tyr Lys Leu Asn Ala Val Ala
```

```
    530                 535                 540

Glu Ala Val Leu Lys Asp Lys Lys Lys Asp Leu Ser Tyr Arg Asp Ile
545                 550                 555                 560

Pro Thr Tyr Tyr Ala Ala Gly Pro Ala Gln Arg Gly Val Ile Gly Glu
                565                 570                 575

Tyr Cys Ile Gln Asp Ser Leu Leu Val Gly Gln Leu Phe Phe Lys Phe
            580                 585                 590

Leu Pro His Leu Glu Leu Ser Ala Val Ala Arg Leu Ala Gly Ile Asn
        595                 600                 605

Ile Thr Arg Thr Ile Tyr Asp Gly Gln Gln Ile Arg Val Phe Thr Cys
    610                 615                 620

Leu Leu Arg Leu Ala Asp Gln Lys Gly Phe Ile Leu Pro Asp Thr Gln
625                 630                 635                 640

Gly Arg Phe Arg Gly Ala Gly Gly Glu Ala Pro Lys Arg Pro Ala Ala
                645                 650                 655

Ala Arg Glu Asp Glu Glu Arg Pro Glu Glu Glu Gly Glu Asp Glu Asn
            660                 665                 670

Glu Arg Glu Glu Gly Gly Gly Glu Arg Glu Pro Glu Gly Ala Arg Glu
        675                 680                 685

Thr Ala Gly Arg His Val Gly Tyr Gln Gly Ala Arg Val Leu Asp Pro
    690                 695                 700

Thr Ser Gly Phe His Val Asn Pro Val Val Val Phe Asp Phe Ala Ser
705                 710                 715                 720

Leu Tyr Pro Ser Ile Ile Gln Ala His Asn Leu Cys Phe Ser Thr Leu
                725                 730                 735

Ser Leu Arg Ala Asp Ala Val Ala His Leu Glu Ala Gly Lys Asp Tyr
            740                 745                 750

Leu Glu Ile Glu Val Gly Gly Arg Arg Leu Phe Phe Val Lys Ala His
        755                 760                 765

Val Arg Glu Ser Leu Leu Ser Ile Leu Leu Arg Asp Trp Leu Ala Met
    770                 775                 780

Arg Lys Gln Ile Arg Ser Arg Ile Pro Gln Ser Ser Pro Glu Glu Ala
785                 790                 795                 800

Val Leu Leu Asp Lys Gln Gln Ala Ala Ile Lys Val Val Cys Asn Ser
                805                 810                 815

Val Tyr Gly Phe Thr Gly Val Gln His Gly Leu Leu Pro Cys Leu His
            820                 825                 830

Val Ala Ala Thr Val Thr Thr Ile Gly Arg Glu Met Leu Leu Ala Thr
        835                 840                 845

Arg Glu Tyr Val His Ala Arg Trp Ala Ala Phe Glu Gln Leu Leu Ala
    850                 855                 860
```

```
Asp Phe Pro Glu Ala Ala Asp Met Arg Ala Pro Gly Pro Tyr Ser Met
865                 870                 875                 880

Arg Ile Ile Tyr Gly Asp Thr Asp Ser Ile Phe Val Leu Cys Arg Gly
                885                 890                 895

Leu Thr Ala Ala Gly Leu Thr Ala Val Gly Asp Lys Met Ala Ser His
            900                 905                 910

Ile Ser Arg Ala Leu Phe Leu Pro Pro Ile Lys Leu Glu Cys Glu Lys
        915                 920                 925

Thr Phe Thr Lys Leu Leu Leu Ile Ala Lys Lys Lys Tyr Ile Gly Val
    930                 935                 940

Ile Tyr Gly Gly Lys Met Leu Ile Lys Gly Val Asp Leu Val Arg Lys
945                 950                 955                 960

Asn Asn Cys Ala Phe Ile Asn Arg Thr Ser Arg Ala Leu Val Asp Leu
                965                 970                 975

Leu Phe Tyr Asp Asp Thr Val Ser Gly Ala Ala Ala Ala Leu Ala Glu
            980                 985                 990

Arg Pro Ala Glu Glu Trp Leu Ala  Arg Pro Leu Pro Glu  Gly Leu Gln
        995                 1000                1005

Ala Phe  Gly Ala Val Leu Val  Asp Ala His Arg Arg  Ile Thr Asp
    1010                1015                1020

Pro Glu  Arg Asp Ile Gln Asp  Phe Val Leu Thr Ala  Glu Leu Ser
    1025                1030                1035

Arg His  Pro Arg Ala Tyr Thr  Asn Lys Arg Leu Ala  His Leu Thr
    1040                1045                1050

Val Tyr  Tyr Lys Leu Met Ala  Arg Arg Ala Gln Val  Pro Ser Ile
    1055                1060                1065

Lys Asp  Arg Ile Pro Tyr Val  Ile Val Ala Gln Thr  Arg Glu Val
    1070                1075                1080

Glu Glu  Thr Val Ala Arg Leu  Ala Ala Leu Arg Glu  Leu Asp Ala
    1085                1090                1095

Ala Ala  Pro Gly Asp Glu Pro  Ala Pro Pro Ala Ala  Leu Pro Ser
    1100                1105                1110

Pro Ala  Lys Arg Pro Arg Glu  Thr Pro Ser Pro Ala  Asp Pro Pro
    1115                1120                1125

Gly Gly  Ala Ser Lys Pro Arg  Lys Leu Leu Val Ser  Glu Leu Ala
    1130                1135                1140

Glu Asp  Pro Ala Tyr Ala Ile  Ala His Gly Val Ala  Leu Asn Thr
    1145                1150                1155

Asp Tyr  Tyr Phe Ser His Leu  Leu Gly Ala Ala Cys  Val Thr Phe
    1160                1165                1170

Lys Ala  Leu Phe Gly Asn Asn  Ala Lys Ile Thr Glu  Ser Leu Leu
    1175                1180                1185
```

```
Lys Arg  Phe Ile Pro Glu Val  Trp His Pro Pro Asp  Asp Val Ala
    1190                 1195                 1200

Ala Arg  Leu Arg Thr Ala Gly  Phe Gly Ala Val Gly  Ala Gly Ala
    1205                 1210                 1215

Thr Ala  Glu Glu Thr Arg Arg  Met Leu His Arg Ala  Phe Asp Thr
    1220                 1225                 1230

Leu Ala
    1235
```

<210> 19
<211> 1235
<212> PRT
<213> herpes simplex

<400> 19

```
Met Phe Ser Gly Gly Gly Gly Pro Leu Ser Pro Gly Gly Lys Ser Ala
1               5                  10                  15

Ala Arg Ala Ala Ser Gly Phe Phe Ala Pro Ala Gly Pro Arg Gly Ala
            20                  25                  30

Gly Arg Gly Pro Pro Pro Cys Leu Arg Gln Asn Phe Tyr Asn Pro Tyr
        35                  40                  45

Leu Ala Pro Val Gly Thr Gln Gln Lys Pro Thr Gly Pro Thr Gln Arg
    50                  55                  60

His Thr Tyr Tyr Ser Glu Cys Asp Glu Phe Arg Phe Ile Ala Pro Arg
65                  70                  75                  80

Val Leu Asp Glu Asp Ala Pro Pro Glu Lys Arg Ala Gly Val His Asp
                85                  90                  95

Gly His Leu Lys Arg Ala Pro Lys Val Tyr Cys Gly Gly Asp Glu Arg
            100                 105                 110

Asp Val Leu Arg Val Gly Ser Gly Gly Phe Trp Pro Arg Arg Ser Arg
        115                 120                 125

Leu Trp Gly Gly Val Asp His Ala Pro Ala Gly Phe Asn Pro Thr Val
    130                 135                 140

Thr Val Phe His Val Tyr Asp Ile Leu Glu Asn Val Glu His Ala Tyr
145                 150                 155                 160

Gly Met Arg Ala Ala Gln Phe His Ala Arg Phe Met Asp Ala Ile Thr
                165                 170                 175

Pro Thr Gly Thr Val Ile Thr Leu Leu Gly Leu Thr Pro Glu Gly His
            180                 185                 190

Arg Val Ala Val His Val Tyr Gly Thr Arg Gln Tyr Phe Tyr Met Asn
        195                 200                 205

Lys Glu Glu Val Asp Arg His Leu Gln Cys Arg Ala Pro Arg Asp Leu
    210                 215                 220
```

```
Cys Glu Arg Met Ala Ala Ala Leu Arg Glu Ser Pro Gly Ala Ser Phe
225                 230                 235                 240

Arg Gly Ile Ser Ala Asp His Phe Glu Ala Glu Val Val Glu Arg Thr
                245                 250                 255

Asp Val Tyr Tyr Tyr Glu Thr Arg Pro Ala Leu Phe Tyr Arg Val Tyr
            260                 265                 270

Val Arg Ser Gly Arg Val Leu Ser Tyr Leu Cys Asp Asn Phe Cys Pro
        275                 280                 285

Ala Ile Lys Lys Tyr Glu Gly Gly Val Asp Ala Thr Thr Arg Phe Ile
    290                 295                 300

Leu Asp Asn Pro Gly Phe Val Thr Phe Gly Trp Tyr Arg Leu Lys Pro
305                 310                 315                 320

Gly Arg Asn Asn Thr Leu Ala Gln Pro Arg Ala Pro Met Ala Phe Gly
                325                 330                 335

Thr Ser Ser Asp Val Glu Phe Asn Cys Thr Ala Asp Asn Leu Ala Ile
            340                 345                 350

Glu Gly Gly Met Ser Asp Leu Pro Ala Tyr Lys Leu Met Cys Phe Asp
        355                 360                 365

Ile Glu Cys Lys Ala Gly Gly Glu Asp Glu Leu Ala Phe Pro Val Ala
    370                 375                 380

Gly His Pro Glu Asp Leu Val Ile Gln Ile Ser Cys Leu Leu Tyr Asp
385                 390                 395                 400

Leu Ser Thr Thr Ala Leu Glu His Val Leu Leu Phe Ser Leu Gly Ser
                405                 410                 415

Cys Asp Leu Pro Glu Ser His Leu Asn Glu Leu Ala Ala Arg Gly Leu
            420                 425                 430

Pro Thr Pro Val Val Leu Glu Phe Asp Ser Glu Phe Glu Met Leu Leu
        435                 440                 445

Ala Phe Met Thr Leu Val Lys Gln Tyr Gly Pro Glu Phe Val Thr Gly
    450                 455                 460

Tyr Asn Ile Ile Asn Phe Asp Trp Pro Phe Leu Leu Ala Lys Leu Thr
465                 470                 475                 480

Asp Ile Tyr Lys Val Pro Leu Asp Gly Tyr Gly Arg Met Asn Gly Arg
                485                 490                 495

Gly Val Phe Arg Val Trp Asp Ile Gly Gln Ser His Phe Gln Lys Arg
            500                 505                 510

Ser Lys Ile Lys Val Asn Gly Met Val Asn Ile Asp Met Tyr Gly Ile
        515                 520                 525

Ile Thr Asp Lys Ile Lys Leu Ser Ser Tyr Lys Leu Asn Ala Val Ala
    530                 535                 540

Glu Ala Val Leu Lys Asp Lys Lys Lys Asp Leu Ser Tyr Arg Asp Ile
545                 550                 555                 560
```

```
Pro Ala Tyr Tyr Ala Ala Gly Pro Ala Gln Arg Gly Val Ile Gly Glu
                565                 570                 575

Tyr Cys Ile Gln Asp Ser Leu Leu Val Gly Gln Leu Phe Phe Lys Phe
            580                 585                 590

Leu Pro His Leu Glu Leu Ser Ala Val Ala Arg Leu Ala Gly Ile Asn
        595                 600                 605

Ile Thr Arg Thr Ile Tyr Asp Gly Gln Gln Ile Arg Val Phe Thr Cys
    610                 615                 620

Leu Leu Arg Leu Ala Asp Gln Lys Gly Phe Ile Leu Pro Asp Thr Gln
625                 630                 635                 640

Gly Arg Phe Arg Gly Gly Gly Gly Glu Ala Pro Lys Arg Pro Ala Ala
                645                 650                 655

Ala Arg Glu Asp Glu Glu Arg Pro Glu Glu Glu Gly Glu Asp Glu Asp
            660                 665                 670

Glu Arg Glu Glu Gly Gly Gly Glu Arg Glu Pro Glu Gly Ala Arg Glu
        675                 680                 685

Thr Ala Gly Arg His Val Gly Tyr Gln Gly Ala Arg Val Leu Asp Pro
    690                 695                 700

Thr Ser Gly Phe His Val Asn Pro Val Val Val Phe Asp Phe Ala Ser
705                 710                 715                 720

Leu Tyr Pro Ser Ile Ile Gln Ala His Asn Leu Cys Phe Ser Thr Leu
                725                 730                 735

Ser Leu Arg Ala Asp Ala Val Ala His Leu Glu Ala Gly Lys Asp Tyr
            740                 745                 750

Leu Glu Ile Glu Val Gly Gly Arg Arg Leu Phe Phe Val Lys Ala His
        755                 760                 765

Val Arg Glu Ser Leu Leu Ser Ile Leu Leu Arg Asp Trp Leu Ala Met
    770                 775                 780

Arg Lys Gln Ile Arg Ser Arg Ile Pro Gln Ser Ser Pro Glu Glu Ala
785                 790                 795                 800

Val Leu Leu Asp Lys Gln Gln Ala Ala Ile Lys Val Val Cys Asn Ser
                805                 810                 815

Val Tyr Gly Phe Thr Gly Val Gln His Gly Leu Leu Pro Cys Leu His
            820                 825                 830

Val Ala Ala Thr Val Thr Thr Ile Gly Arg Glu Met Leu Leu Ala Thr
        835                 840                 845

Arg Glu Tyr Val His Ala Arg Trp Ala Ala Phe Glu Gln Leu Leu Ala
    850                 855                 860

Asp Phe Pro Glu Ala Ala Asp Met Arg Ala Pro Gly Pro Tyr Ser Met
865                 870                 875                 880

Arg Ile Ile Tyr Gly Asp Thr Asp Ser Ile Phe Val Leu Cys Arg Gly
```

```
                885                 890                 895

Leu Thr Ala Ala Gly Leu Thr Ala Val Gly Asp Lys Met Ala Ser His
            900                 905                 910

Ile Ser Arg Ala Leu Phe Leu Ser Pro Ile Lys Leu Glu Cys Glu Lys
        915                 920                 925

Thr Phe Thr Lys Leu Leu Leu Ile Ala Lys Lys Lys Tyr Ile Gly Val
    930                 935                 940

Ile Tyr Gly Gly Lys Met Leu Ile Lys Gly Val Asp Leu Val Arg Lys
945                 950                 955                 960

Asn Asn Cys Ala Phe Ile Asn Arg Thr Ser Arg Ala Leu Val Asp Leu
                965                 970                 975

Leu Phe Tyr Asp Asp Thr Val Ser Gly Ala Ala Ala Ala Leu Ala Glu
            980                 985                 990

Arg Pro Ala Glu Glu Trp Leu Ala  Arg Pro Leu Pro Glu  Gly Leu Gln
        995                 1000                1005

Ala Phe  Gly Ala Val Leu Val  Asp Ala His Arg Arg  Ile Thr Asp
    1010                1015                1020

Pro Glu  Arg Asp Ile Gln Asp  Phe Val Leu Thr Ala  Glu Leu Ser
    1025                1030                1035

Arg His  Pro Arg Ala Tyr Thr  Asn Lys Arg Leu Ala  His Leu Thr
    1040                1045                1050

Val Tyr  Tyr Lys Leu Met Ala  Arg Arg Ala Gln Val  Pro Ser Ile
    1055                1060                1065

Lys Asp  Arg Ile Pro Tyr Val  Ile Val Ala Gln Thr  Arg Glu Val
    1070                1075                1080

Glu Glu  Thr Val Ala Arg Leu  Ala Ala Leu Arg Glu  Leu Asp Ala
    1085                1090                1095

Ala Ala  Pro Gly Asp Glu Pro  Ala Pro Pro Ala Ala  Leu Pro Ser
    1100                1105                1110

Pro Ala  Lys Arg Pro Arg Glu  Thr Pro Leu His Ala  Asp Pro Pro
    1115                1120                1125

Gly Gly  Ala Ser Lys Pro Arg  Lys Leu Leu Val Ser  Glu Leu Ala
    1130                1135                1140

Glu Asp  Pro Ala Tyr Ala Ile  Ala His Gly Val Ala  Leu Asn Thr
    1145                1150                1155

Asp Tyr  Tyr Phe Ser His Leu  Leu Gly Ala Ala Cys  Val Thr Phe
    1160                1165                1170

Lys Ala  Leu Phe Gly Asn Asn  Ala Lys Ile Thr Glu  Ser Leu Leu
    1175                1180                1185

Lys Arg  Phe Ile Pro Glu Val  Trp His Pro Pro Asp  Asp Val Ala
    1190                1195                1200
```

```
Ala Arg  Leu Arg Ala Ala Gly  Phe Gly Ala Val Gly  Ala Gly Ala
    1205                 1210                 1215

Thr Ala  Glu Glu Thr Arg Arg  Met Leu His Arg Ala  Phe Asp Thr
    1220                 1225                 1230

Leu Ala
    1235
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(10) International Publication Number
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23 January 2003

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 02/006513 A3

(54) Title: A METHOD FOR TREATING HERPES VIRUSES

(57) Abstract: The present invention relates to a method for selecting an anti-herpes viral compound and a method for selectively inhibiting herpesvrus in a human host in need of such treatment. The present invention relates to a method for selecting an anti-herpes viral compound and a method for selectively inhibiting herpsvrus in a human host in need of such treatment.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 01/16525

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 G01N33/569 A61P31/22 C07K14/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 G01N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 097 633 A (SUNDQVIST VIVI ANNE ;WAHREN BRITTA (SE); HARMENBERG JOHAN (SE)) 4 January 1984 (1984-01-04) the whole document ---	1,2,4,5, 8,9,11, 12,16, 17,20, 23-26
A	WO 98 04707 A (MCLEAN GORDON WILLIAM ;MEDICAL RES COUNCIL (GB); STOW NIGEL DENNIS) 5 February 1998 (1998-02-05) abstract --- -/--	1,2,4,5, 8,9,11, 12,16, 17,20, 23-26

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

'A' document defining the general state of the art which is not considered to be of particular relevance

'E' earlier document but published on or after the international filing date

'L' document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

'O' document referring to an oral disclosure, use, exhibition or other means

'P' document published prior to the international filing date but later than the priority date claimed

'T' later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

'X' document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

'Y' document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

'&' document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
30 September 2002	07/10/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Moreno, C

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,A	WO 00 40563 A (STROHBACH JOSEPH WALTER ;SCOTT ALLEN (US); UPJOHN CO (US); SCHNUTE) 13 July 2000 (2000-07-13) abstract ---	1,2,4,5, 8,9,11, 12,16, 17,20, 23-26
P,A	WO 00 40561 A (STROHBACH JOSEPH WALTER ;UPJOHN CO (US); SCHNUTE MARK E (US); THAI) 13 July 2000 (2000-07-13) abstract ---	1,2,4,5, 8,9,11, 12,16, 17,20, 23-26
A	WO 94 24296 A (UNIV SASKATCHEWAN) 27 October 1994 (1994-10-27) abstract -----	25,26

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 01/16525

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

Continuation of Box I.2

Present claims 23 and 24 relate to a compound defined by reference to a desirable characteristic or property, namely the change of the wild type HSV-1 polymerases at amino acid 823 from valine to alanine in the presence of said compound.

The claims cover all compounds having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compound by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the compounds 1-17 in figure 1.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 01/16525

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